Ketene dithioacetals in synthesis

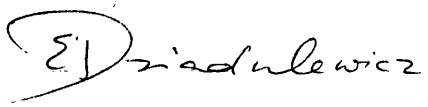
Dziadulewicz, E. K.

Award date:
1987

Awarding institution:
University of Bath

KETENE DITHIOACETALS IN SYNTHESIS

Submitted by E. K. Dziadulewicz
for the degree of PhD
of the University of Bath
1987



E. K. Dziadulewicz

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

To my parents, for their constant

support and encouragement.

ACKNOWLEDGEMENTS

The work described in this thesis was undertaken at the University of Bath from October 1983 to November 1986.

I would like to thank my supervisor, Dr Tim Gallagher for his patience, guidance, and for supplying "motivation at the end of my boot" at those disheartening moments when black tars ruled the day, and a job with the local council's road-resurfacing division loomed on the horizon.

The technical support staff also merit thanks. The laboratory technicians: Mrs S. Boucher, Mr R. Hunter and Mr R. Betteridge, who made the practical work possible; and the spectroscopic services: Mr D. Wood and Mr H. Hartell (^{1}H and ^{13}C NMR spectroscopy), Mr C. Cryer (mass spectrometry), and Mr A. Carver (elemental microanalysis).

I would also like to express my thanks to colleagues and friends for many helpful discussions, especially Dr D. Lathbury, and my co-workers on different aspects of this project, D. M. Hodgson and M. Giles.

Professor A. McKervey, University College, Cork, is gratefully acknowledged for supplying a sample of 1, 3, 3 - tris (phenylthio) -1- propene (309) for comparative alkylation studies.

Thanks are also due to Mrs P. Kielthy, Mrs E. Wharton and Mrs S. Biggs for some alchemy of their own; that of converting my manuscript to typescript, in a process that has been both qualitative and free of thiol odours.

Finally, I would like to thank the University of Bath for providing research facilities, and the SERC for provision of a research studentship: Bath has presented an ideal setting for memorable and extremely enjoyable student days.

Abstract

This thesis is introduced by a comprehensive review of the major methods employed to functionalise the enone or acrylate structural unit at C-2 and C-3. Creation of a donor, anionic site at C-2 is electronically permissible, but is not attended without difficulties. The same operation at C-3 involves inverting the natural acceptor reactivity via use of synthetically equivalent reagents.

In Section 2, the synthesis and metallation of a novel ketene dithioacetal is described. Lithiation of 1,1-bis(phenylthio)-3-phenylthio-1-propene and reaction with a variety of electrophiles gave exclusively the γ-substituted products. Its use as a β-lithioacrylate equivalent in the construction of butenolides and γ-lactones, is exemplified by a short synthesis of the long range sex attractant pheromone, ($\pm$)-eldanolide.

A range of 1,1,3-trissulphur-substituted propenes was subsequently alkylated, and a study made of their regiochemical preferences; the predominance of α- or γ-regioselectivity being dependent on the type of heteroatom substituents present. Bulky sulphur substituents at the α-carbon atom, such as phenyl, directed reaction to the γ-site. In those compounds in which steric effects were not so pronounced, reaction at the γ-site could be reinforced electronically by incorporating an alkyl or arylthio group at C-3.

The feasibility of alkylating 1,1,3,3 -tetrakis (alkylthio)propenes was also tested. Successful reaction was only achieved with a novel bisdithiane-substituted propene. The acyclic analogues studied were all too sterically encumbered to accommodate electrophiles. This study was concluded with a synthesis of (±)-dihydrokawain, a plant constituent possessing a 5,6-dihydro-4-alkoxy-2H-pyran-2-one skeleton. The equivalency between the lithiated bisdithiane compound and ß-hydroxy -ß-lithioacrylate anion has been thereby established.

ABBREVIATIONS

The following abbreviations are used in the text:

DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0.]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMPU	N,N-Dimethylpropylene urea
DMSO	Dimethyl sulphoxide
HMPA	Hexamethylphosphoric triamide
LDA	Lithium N,N-diisopropylamide
M	Molar
MCPBA	meta-Chloroperoxybenzoic acid
MEM	Methoxyethoxymethylene, $CH_3OCH_2CH_2OCH_2$-
MOM	Methoxymethylene, CH_3OCH_2-
MTM	Methylthiomethylene, CH_3SCH_2-
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
PTSA	para-Toluene sulphonic acid
py	Pyridine
Rf	Retention factor

ABBREVIATIONS

TBDMSCl	*tert*-Butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
TMEDA	*N*,*N*,*N*',*N*'-Tetramethyl ethylene diamine
TMSCl	Trimethylsilyl chloride

CONTENTS

INTRODUCTION

1. INTRODUCTION

1.1 The Concept of Synthetic Equivalency

For the synthesis of complex molecules, it is sometimes desirable to have a specific reagent for the introduction of a given fragment or structural unit. The compound or idealised intermediate actually required to carry out the direct synthetic operation may be inaccessible by normal or direct means, or intrinsically unstable. An effective strategy for the broadening of techniques for assembling collections of carbon atoms and functional groups is to use synthetically equivalent reagents or reaction series to perform identical transformations to these hypothetical compounds. The introduction of intact synthetically equivalent units is inherently attractive, because of the greater degree of convergency associated with this approach, a given unit often being supplied in a conveniently protected form. This latter feature is an important consideration in multistep syntheses of complex natural products, especially in the light of the high reactivity of some components, notably α,β-unsaturated acid derivatives.

Masking of a functional group may help to moderate the reactivity of a reagent, making it useable in the first instance, perhaps eliminating side reactions which might operate in the unmasked form. On the other hand, it is sometimes desirable to have synthons exhibiting reverse polarity at their reactive centres, to extend the general methodology of organic synthesis. These requirements must be translated into the design of reagents for practical use, and in Sections 1.2.2 and 1.2.3.2, the design of donor nucleophilic

sites at C-2, and the normally acceptor C-3 of the acrylate or enone unit is considered, *via* synthetically equivalent reagents.

1.2 The Functionalisation of the Acrylate Unit and Related Derivatives

1.2.1 Introduction

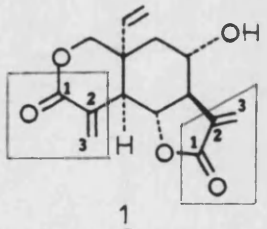
The routine use, and widespread applicability, of the enone or acrylate moiety in carbon-carbon bond forming processes has a tendency to belie its importance in everyday synthetic operations. The possession of acceptor and dienophile properties, however, makes it a valuable synthetic agency in the construction or elaboration of organic molecules.[1] The fact that a relatively uncomplicated three-carbon unit can be functionalised at each carbon atom, potentially incorporating a total of four substituents, endows it with a versatility that has been utilised and expressed in another, more fundamental respect.

The acrylate unit and related groups are ubiquitous in nature as structural features of a very large number of secondary metabolites, many of which possess useful biological activity.[2] The exploitation of this activity is extremely desirable from a pharmaceutical viewpoint; the extension of the number of structural analogues which demonstrate or supercede it therefore has a medicinal and commercial incentive. Yet, this endeavour is also academically stimulating, necessarily generating new reagents and new methodology: the raw materials for future synthetic applications.

Retrosynthetic strategy in the design of these natural products often reveals the acrylate unit, albeit in masked or protected form, at different levels of oxidation, and varying in its point of

attachment to the remaining carbon framework. Included among these compounds are several classes of saturated and unsaturated carboxylic acids, esters, and lactones, and a few representative examples will serve to illustrate the manner in which this unit is employed in their architecture.

The most commonly occurring acrylate derivatives are the very well known α-methylenelactones. In particular, the α-methylene-γ-butyrolactone ring is an integral building block of many natural products, especially the sesquiterpene lactones.[3] Compounds such as the potent tumour-inhibiting agent vernolepin 1,[4,5] and eremophildienoic acid 2,[6] in which further rearrangement and oxidative modification have been abandoned in favour of a simple structure, contain an α-substituted acrylate moiety. Indeed, the revelation



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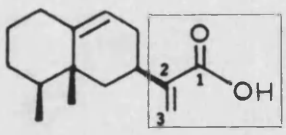
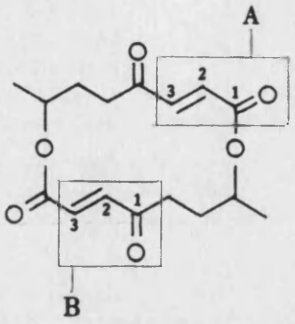


2

of a novel α-lithioacrylate equivalent in the literature is often followed precisely by a synthesis of an α-methylene-γ-butyrolactone carbocyclic derivative: the most obvious synthetic example to which the general methodology can be illustratively applied.

γ- and ε-Oxygenated acrylates and enones are also important features of many natural products, including the macrocyclic antibiotics such as pyrenophorin 3[7] and brefeldin A 4.[8] In these structures, the acrylate unit can be envisaged as being appended at C-3. Another class of compounds incorporating, formally, a β-lithioacrylate derivative are α,β-unsaturated 5- and 6-membered lactones 5, themselves versatile intermediates,[9] as well as



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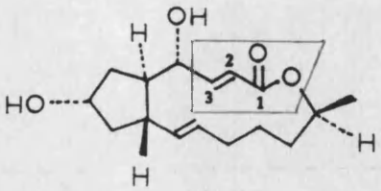

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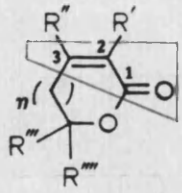
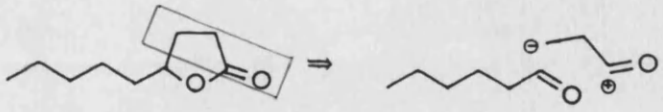


5 n = 0,1

structural features of many biologically important natural products.[10] If saturated lactones, on the other hand, are dissected in a similar way, the adduct can be regarded as a functionalised homoenolate anion equivalent; an example of a naturally-occurring saturated lactone is γ-pelargonolactone 6,[11] well known as a key flavour component of coconut.



6

From a slightly different perspective, the bonding of the enone moiety in pyrenophorin 3 (scheme B, highlighted above) can also be viewed as originating from a hypothetical d^1 centre. However, by utilising the concept of 'umpolung' or 'charge affinity inversion', the normally electrophilic carbonyl or acyl carbon atom is rendered nucleophilic, thus further expanding the synthetic utility of this enone functionality.[12]

The raised profile of some acrylate-incorporating active products has ensured a continued interest in facilitating bond formation from each carbon atom comprising the acrylate or enone unit. In the next few sections, some of the numerous methods developed in recent years for this purpose are reviewed, concentrating on α- and β-functionalisation. This preliminary theme assumes a direct relevance

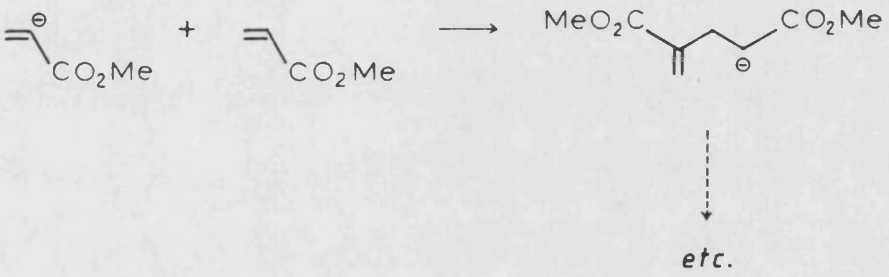
when one considers the role of ketene dithioacetals, the subject of this thesis, as β-lithioacrylate anion equivalents. Ketene dithioacetals generally exhibit an ambident reactivity upon metallation effectively superimposing two anion equivalents of different regioselective preferences on a single ketene dithioacetal framework. In such circumstances, it is difficult to study a single anion equivalent in isolation without the possible intrusion of another, not least at the practical or laboratory level.

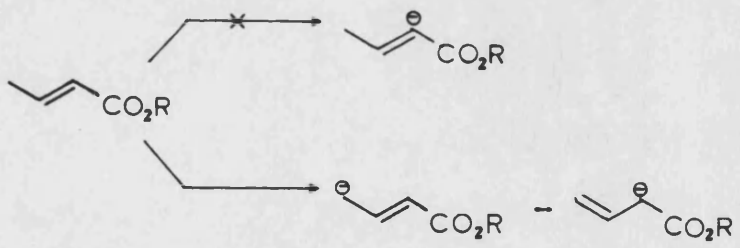
1.2.2 Acrylate Anion d^2 Reagents

Conceptually, one of the most direct approaches for α-functionalisation of acrylic compounds would be the reaction of appropriate electrophilic reagents with, formally speaking, the α-anion. Unlike the d^1 (or d^3) reagents, the formation of a donor, nucleophilic site adjacent to the carbonyl group parallels the normal reactivity imposed at that position by a proximal, 1,3— relationship to the heteroatom. However, the preparation of vinyl carbanions derived from acrylic esters and their reaction with electrophiles are expected to be complicated by the facile involvement of these olefins in Michael additions and their pronounced tendency to undergo anionic polymerisation. The derived vinyl carbanions formed might easily add to the neutral alkene, and, in fact, such a reaction has been reported for acrylic esters.[13] In addition, with more complex target molecules, there are drawbacks in generating carbanionic intermediates under strongly basic conditions.

When considering the alkylation of crotonate esters, closely related to acrylate esters, but possessing a β-methyl group, a further complication arises. In this case, the usefulness of such an α-anionic intermediate has not been generally recognised in

synthetic chemistry. This synthon cannot be directly generated by proton abstraction from C-2, because alk-2-enoic esters having a proton at C-4 afford allyl rather than vinyl anions[13b,14] (see Scheme 1), and this method is used extensively for deconjugative alkylation of such compounds.[15]

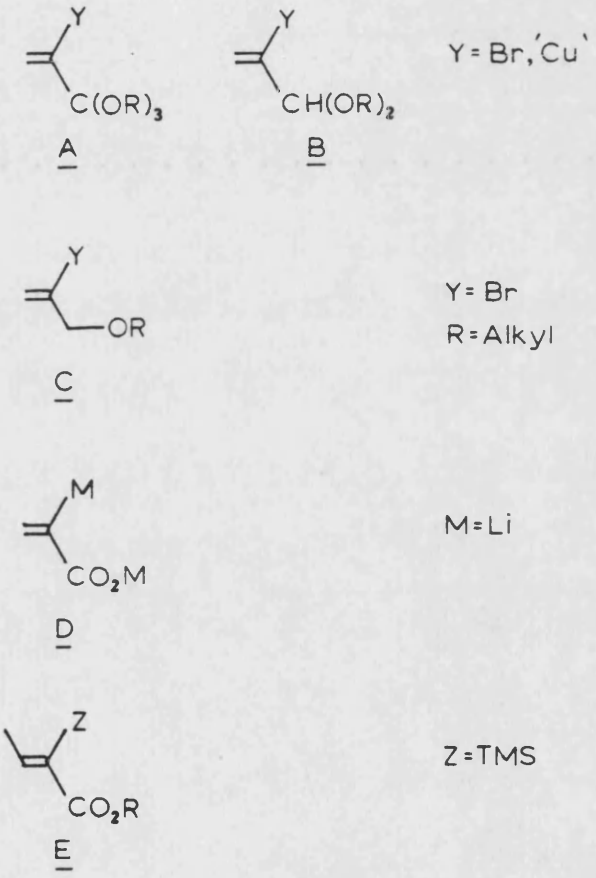




Scheme 1

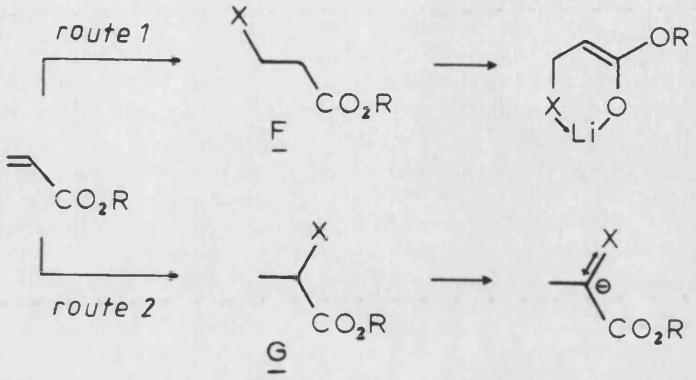
Although a variety of approaches has been used to circumvent the problem of direct α-functionalisation, they are in general of two types. Both categories address themselves to the problem of polymerisation by temporarily masking one or other of the components of the conjugated system.

1. The reactivity of the carbonyl group can be masked by conversion of the ester or aldehyde group into an ortho ester (A) or an acetal (B) respectively, by reduction of the carbonyl moiety (C), or by other methods outlined in Scheme 2.



Scheme 2

2. It is possible to mask the carbon-carbon double bond by adding groups to the α- and β- positions which, after appropriate modification, may ultimately serve as a leaving group in an elimination reaction to re-introduce the α,β-unsaturation after the desired synthetic manipulation has been accomplished (Scheme 3).



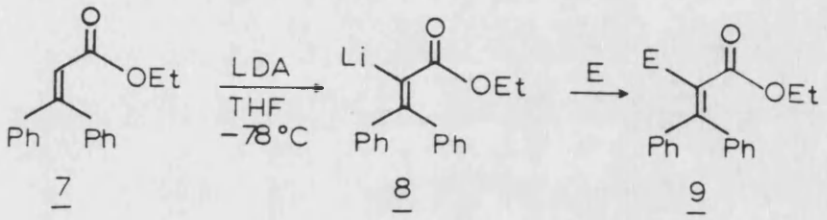
Scheme 3. X = groups capable of elimination.

However, reagents of type F need to meet the requirement of undergoing conversion to the corresponding enolates which can be alkylated with various reagents, but which do not undergo premature elimination. The strategy depicted in Route 1 has an added advantage if the heteroatom (X) can maintain a chelating environment, thereby leading to a stabilised anionic intermediate. Alternatively, the introduction of a negatively-charged group, X^-, in a 1,4- addition simultaneously locates the masking group and anionic centre *in situ*. In Route 2, X behaves as an activating group, and assists in stabilising negative charge.

There are, in addition, some methods which do not rely on the production of an anionic centre, but equally result in α-appended acrylic compounds.

Schmidt *et al.*[13b] were able to derive vinyl carbanions of acrylic ester derivatives without recourse to masking either the

ester carbonyl function, nor the carbon-carbon double bond. The 3,3-diphenyl acrylate 7 could be deprotonated by LDA at -78 °C, and α-substituted derivatives 9 were obtained after reaction with electrophiles (Scheme 4). Use of lithium 2,2,6,6-tetramethyl-piperidine (LTMP) as base prevented the undesirable hydride transfer

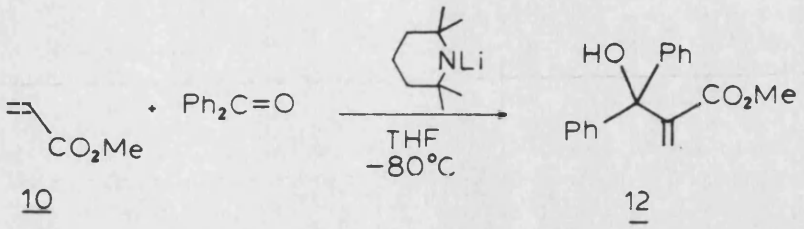


7 8 9

Scheme 4

to the activated carbon-carbon double bond of compounds 9 bearing an electronegative substituent at the α-C atom which resulted, in the case of LDA, in the formation of the corresponding saturated derivatives.

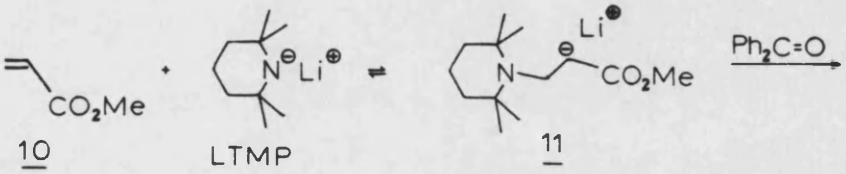
The problem of polymerisation in the case of methyl acrylate was depressed by using excess LTMP. In this instance, a solution of methyl acrylate 10 and benzophenone was added together to a cooled (-80 °C) LTMP-THF solution (Scheme 5), to afford the allyl alcohol 12.



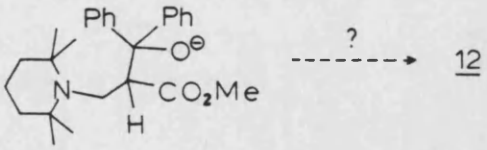
10 12

Scheme 5

By substituting *t*-BuLi for LTMP, Schmidt discounted the possibility that 12 had been formed by activation of 10 in a manner similar to that using DABCO which Hoffmann has employed (see later). The use of *t*-BuLi favoured the vinyl carbanion reaction pathway, because elimination of a *t*-butyl carbanion would be unexpected (Scheme 6).



10 LTMP 11

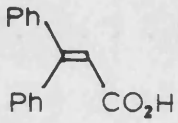


12

Scheme 6

Reaction of the carbanionic intermediate 11 with benzophenone, followed by prototropy (or deprotonation) and elimination would also afford 12.

Boykin *et al.*[16] had reported previously that 13 could not be metallated by *n*-BuLi/THF at -100 °C even in the presence of DABCO. Evidence for the analogous metallation of the ester 14 by LTMP has been described,[17] thus further emphasising the need to protect the acid function. Similarly, all attempts to metallate 15 and 16 *via*



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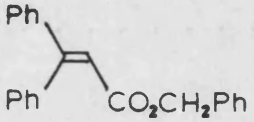

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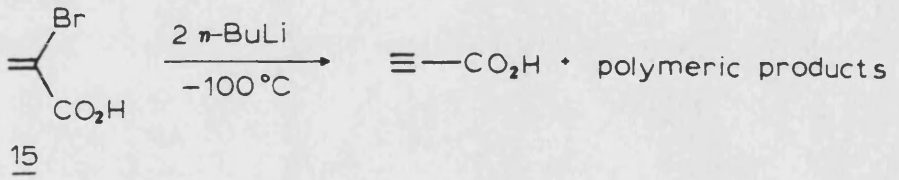
halogen-metal exchange[18] were unsuccessful, giving, at -100 °C, polymeric products[18h] and possibly propiolic acid, by dehydrobromination (Scheme 7).



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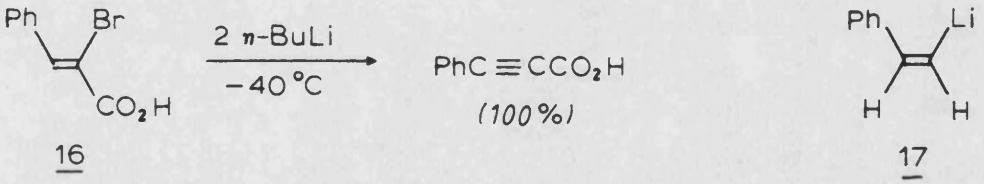


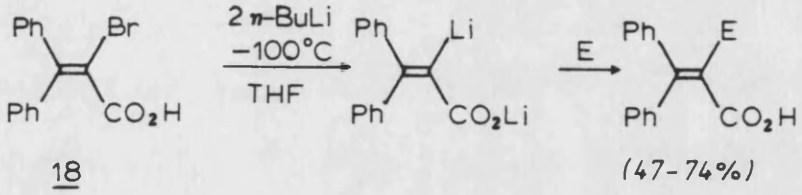
16 17

Scheme 7

Seebach[19] had observed that the intermediate β-lithiostyrene 17, obtained by halogen-metal exchange of β-bromostyrene with two equivalents of *t*-butyl lithium reagent, was stable at -120 °C. However,

at -110 °C, dehydrobromination occurred rapidly, thus confirming Boykin's observations.

By removing the means by which a dehydrobromination mechanism could operate, Boykin[16] was able to metallate 18 at -100 °C, the lithium salt of the carboxylic acid serving adequately as a means of protection[18f,g] (Scheme 8).

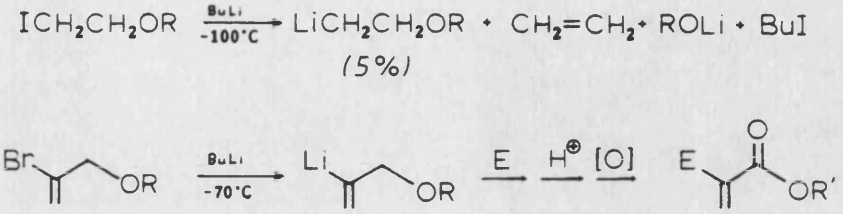


18 (47-74%)

Scheme 8

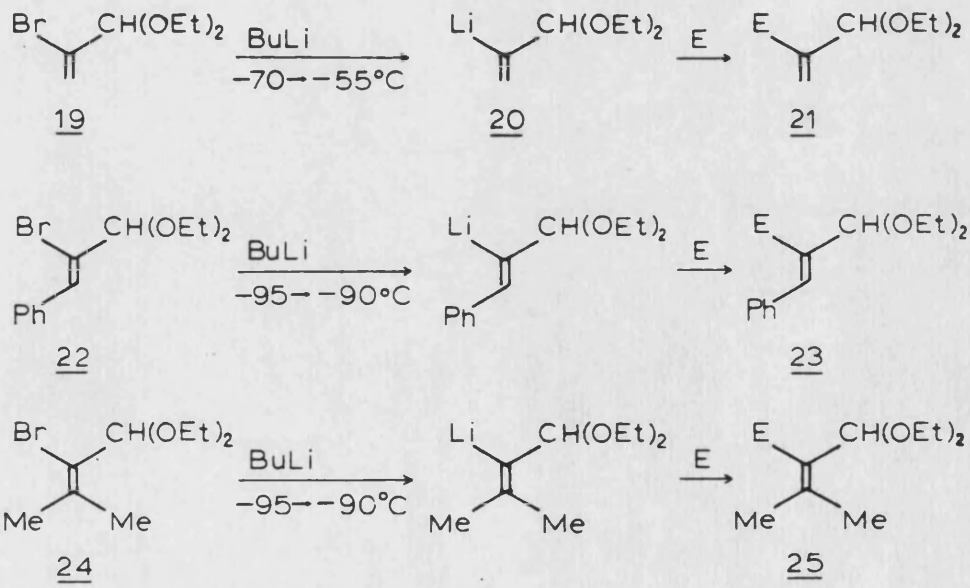
The procedure afforded efficient, good yields of 2-alkylated acrylic acids with most of the electrophilic reagents tested, despite the low yield (47%) with benzophenone. Although not useful for allyl tosylate, oxiranes, usually sluggish in their reactivity, did react; and the methodology was used to construct γ-butyrolactones.

The halogen-metal exchange route to α-functionalised acrylic compounds had been employed ten years prior to Boykin's work by Ficini and Depezay.[20] Ficini had found that unlike saturated iodoalkyl alkyl ethers, where elimination predominated even at -100 °C, the energy of activation of elimination in unsaturated bromoethers is raised. Stable metallated intermediates could therefore be generated at relatively higher temperatures, and oxidation of the free hydroxy products would yield the α-substituted acrylic compounds[21] (Scheme 9).



Scheme 9

Ficini used the diethyl acetal 19 of α-bromoacrolein as an acrylic acid or enone d^2 equivalent, and also examined the reactions of the β-phenyl[18f] 22, and β,β-dimethyl 24 derivatives with a small group of electrophiles (Scheme 10).

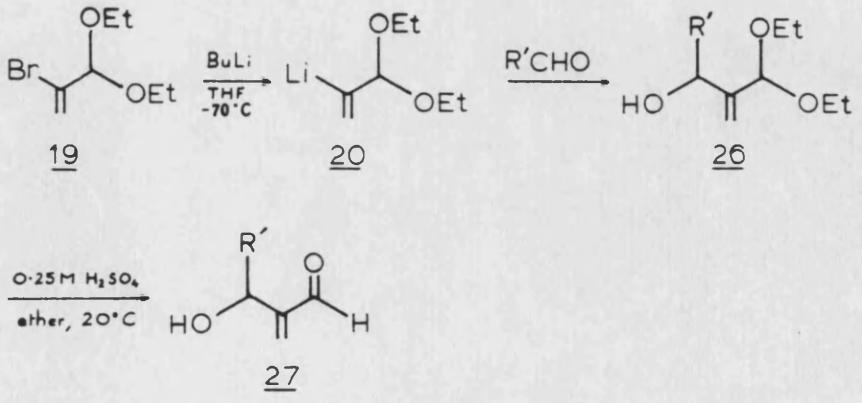


Entry	Electrophile	Yield (%) 21	23	25
a	H_2O	60	55	70
b	CO_2/H_3O^+	50	-	-
c	cyclohexanone	-	50	-

Scheme 10

In comparison to Boykin's work on the free carboxylic acids, the temporary inconvenience of masking a reduced acrylic acid derivative was shown by Ficini to result in substitution instead of elimination, and at a higher reaction temperature (compare reactivities of 19, 22 and 24 with those of 15, 16 and 18 respectively), using only one equivalent of base.

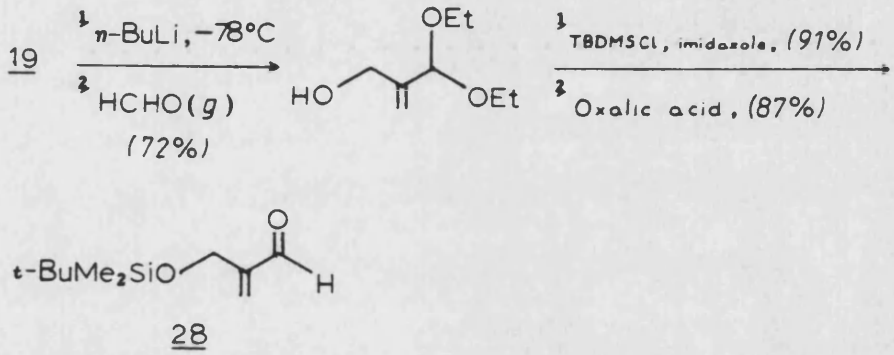
Depezay *et al.*[22] extended the work of Ficini, with simple alkyl and phenyl aldehydes, to afford β-hydroxy aldehydes 27 (Scheme 11). The intermediate α-functionalised acetals 26 were formed in 79-82% yield.



19 20 26 27

Scheme 11

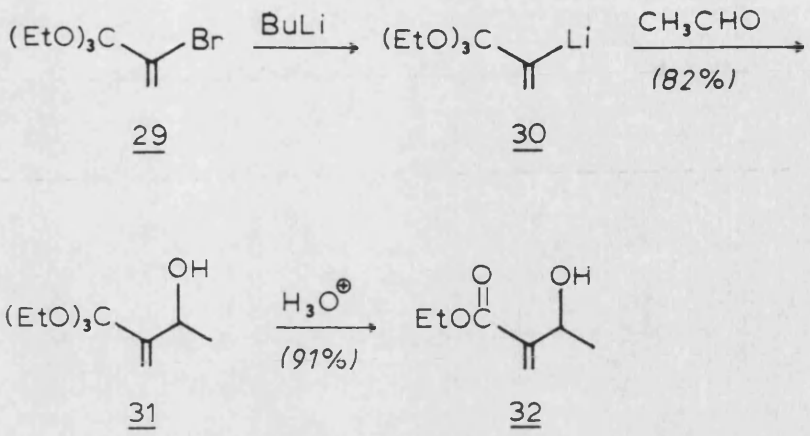
Smith *et al.*[23a,b] in his approach to simple 3(2H)-furanones, required *t*-butyldimethylsiloxymethacrolein[24] 28, and modelled its synthesis after the previous work by Ficini (Scheme 12).



Scheme 12

The other common way of masking the carbonyl functionality (see A, page 7) was demonstrated by Stetter and Uerdingen[25] who reported the synthesis of the ethoxy ortho ester of α-bromoacrylic acid 29. Subsequently, Goldberg and Dreiding[26] reported its metallation and use as an acrylate ester d^2 reagent (Scheme 13). Reaction of 29 with BuLi and acetaldehyde afforded the protected β-hydroxy acrylic compound 31; hydrolysis released the ethyl ester to afford 32 in 91% yield.

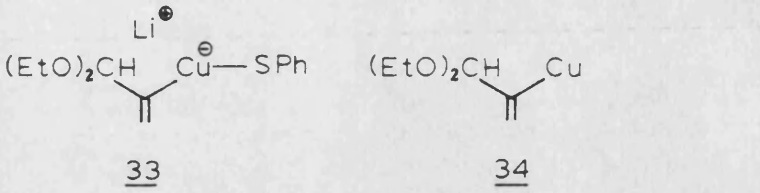
The Ficini-Depezay diethoxy acetal intermediate 20 was also employed by Grieco *et al.*[27] in his efforts to synthesise α-methylene-lactones.[3a] Reaction of 20 with cuprous thiophenoxide in ether at



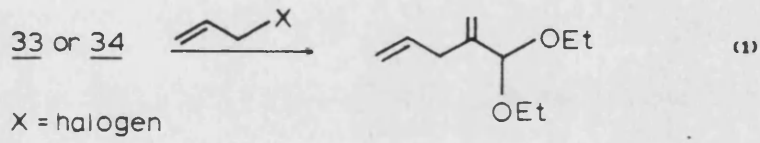
Scheme 13

-78 °C formed the mixed cuprate, phenylthio[(α-diethoxymethyl)vinyl]-cuprate[28] 33. He reported the reactions of 33, and those of (α-diethoxymethyl)vinylcopper[29,30] 34 with allyl, and alkyl halides, an epoxide, and α,β-unsaturated ketones (Scheme 14).

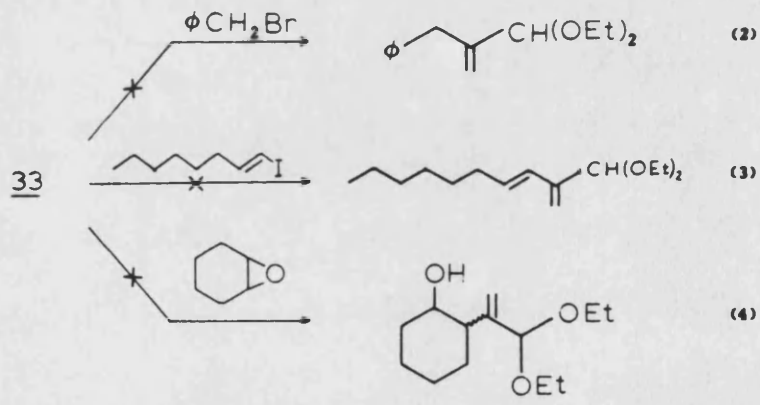
Both 33 and 34 were found to be highly specific for allyl halides, but reaction of 33 with benzyl bromide, (E)-1-iodo oct-1-ene, and cyclohexene epoxide failed. 34, however, did add to cyclohexenone in ether to afford 35 in 90% yield. The isolation of a product of 1,2- addition was somewhat surprising, bearing in mind the normal reactivity of other organocopper reagents with conjugated systems.[31] In contrast, 33 was shown to undergo smooth, conjugate 1,4- addition to cyclohexenone in ether at temperatures below -40 °C to afford 36 in 88% yield. Using this methodology, Grieco was able to synthesise a previously unreported class of δ-valerolactones 37 (Scheme 15).



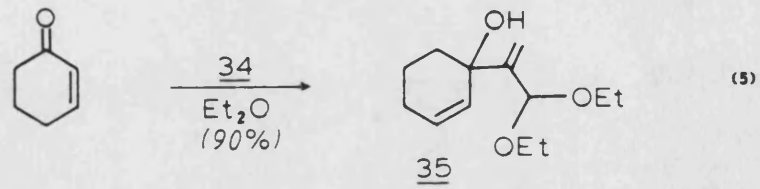
33 34



(1)



(2) (3) (4)



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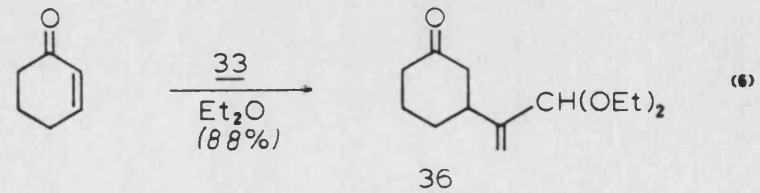
(5)



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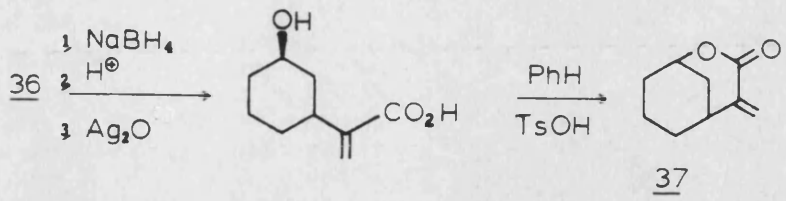
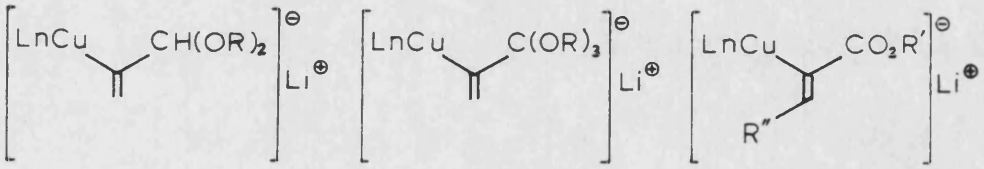
(6)

Scheme 14



Scheme 15

Marino *et al.* also concentrated on organocuprate reagents. Derived from the d^2 building blocks 20 and 30, and from alkyl propiolates, the corresponding cuprates 38,[32a,b] 39[33] and 40[33,34a-d] exhibited different reactivities; the nature of the ligand (Ln), and the terminal, non-vinylic carbon moiety having a profound influence on the cuprate reactivity.

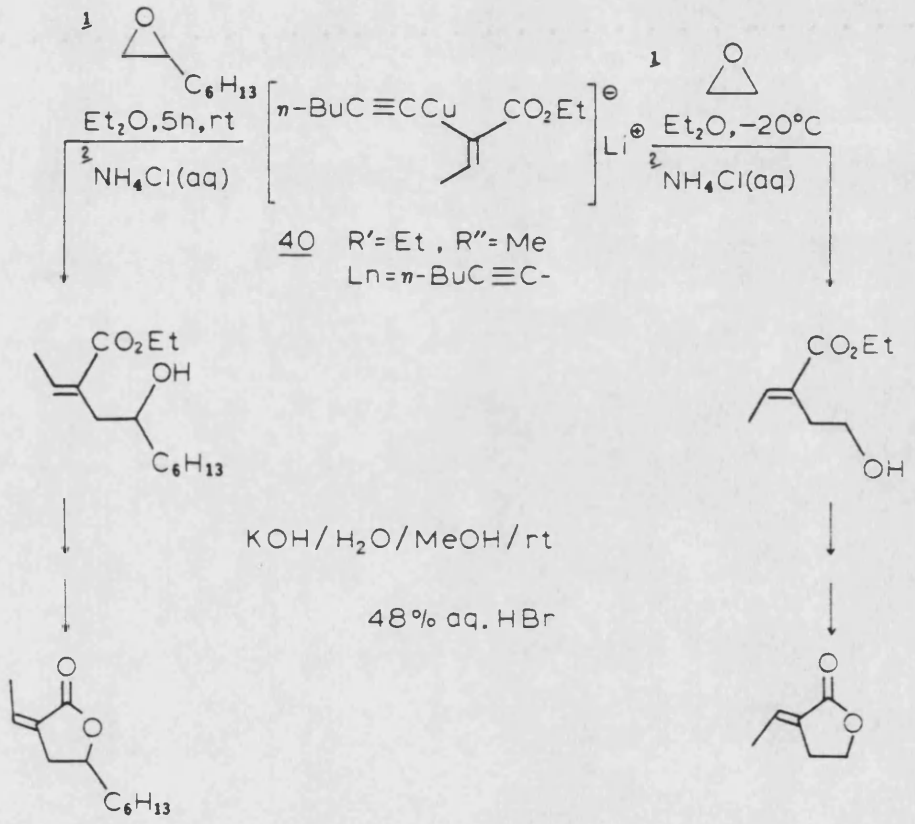


38 39 40

R = Et ; R' = Me,Et ; R" = H,Me.

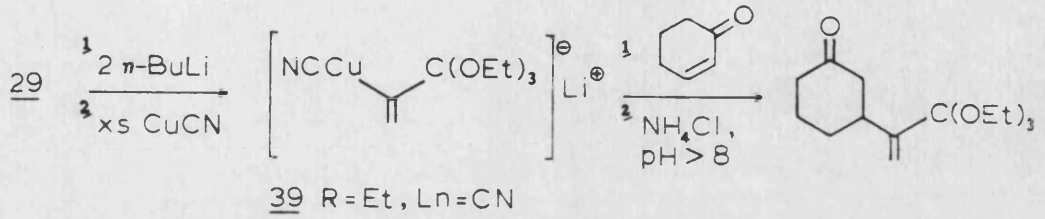
The cuprate reagents 40 were the most extensively studied, and a reactivity pattern with various electrophiles was established.[34e] Reagents 40 were highly specific for allyl, and propargyl halides and showed no reaction with alkyl iodides, iodobenzene, 2-bromopropene, and benzyl bromide.[34a] These cuprates were unable to undergo conjugate addition, and reacted in 1,2- fashion with a series of α,β- unsaturated carbonyl compounds,[34a] this 1,2-

addition reaction having precedent.[31] Marino exploited this reactivity with respect to a cyclopentenone annulation sequence[34b] employing a Nazarov-type cyclisation.[35] In the formation of alkylidene lactones, reaction was found to be limited to acyclic terminal epoxides[33] (Scheme 16).



Scheme 16

In the case of α,β-unsaturated carbonyl compounds, analogous reactivity was observed with other enolisable cuprate reagents of type 40. However, if the ability to enolise was removed, 'normal' cuprate reactivity was restored. The reagents 38[32a] and 39[33] were shown to undergo 1,4- addition to cyclic enones (Scheme 17).

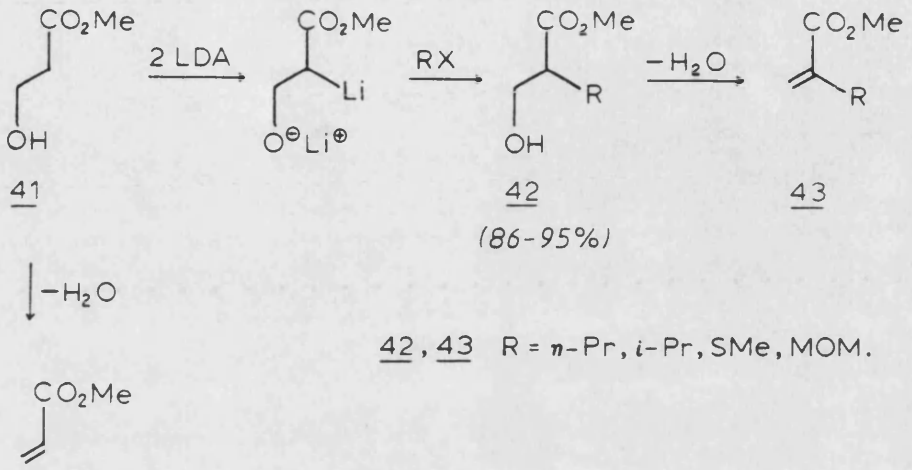


39 R = Et, Ln = CN

Scheme 17

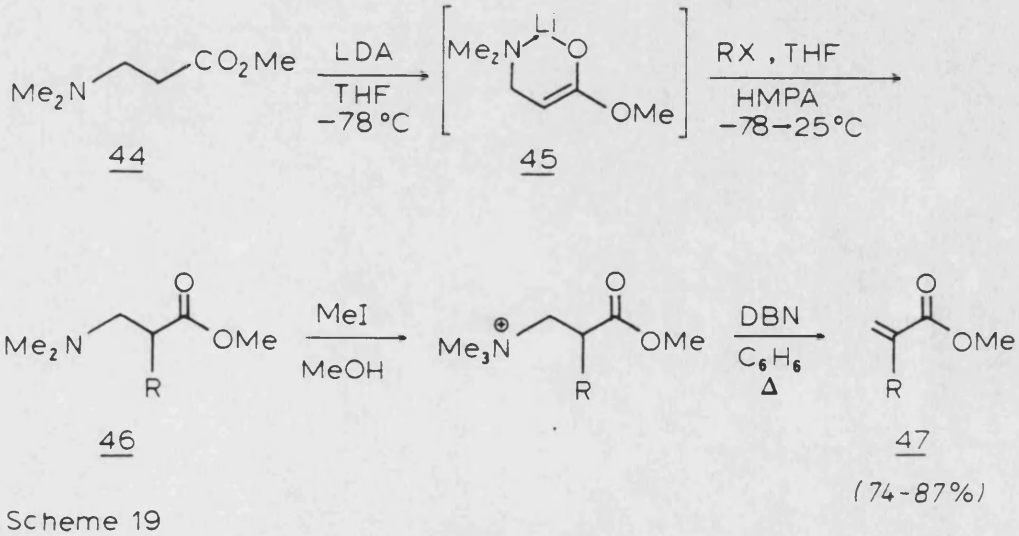
In reaction with simple epoxides it was shown[32b] that reagents 38 were more reactive than the neutral copper (I) reagent 34; the Ficini d^2 reagent 20 did not react with epoxides.

After masking of the double bond, acrylic compounds can also be functionalised. This has been accomplished by Schlessinger *et al.*[36] by employing methyl 3-hydroxypropionate 41, prepared from β-propiolactone in one step in 92% yield.[37] The use of two equivalents of LDA generates the anionic centre and 'protects' the hydroxyl function as the alkoxide. Alkylation occurs at the enolic position to give α-substituted hydroxy esters in 86-95% yield. Dehydration[38] reveals the α,β-unsaturation (Scheme 18). The dehydration reaction has also been applied to lactone systems.[39] Helquist *et al.*[40] used methyl 3-(*N*,*N*-dimethylamino)propionate[41] 44, which is readily available *via* Michael-type addition of dimethylamine to acrylic ester,[42] as a d^2 acrylic building block. Metallation of the ester is facilitated by complexation with nitrogen



Scheme 18

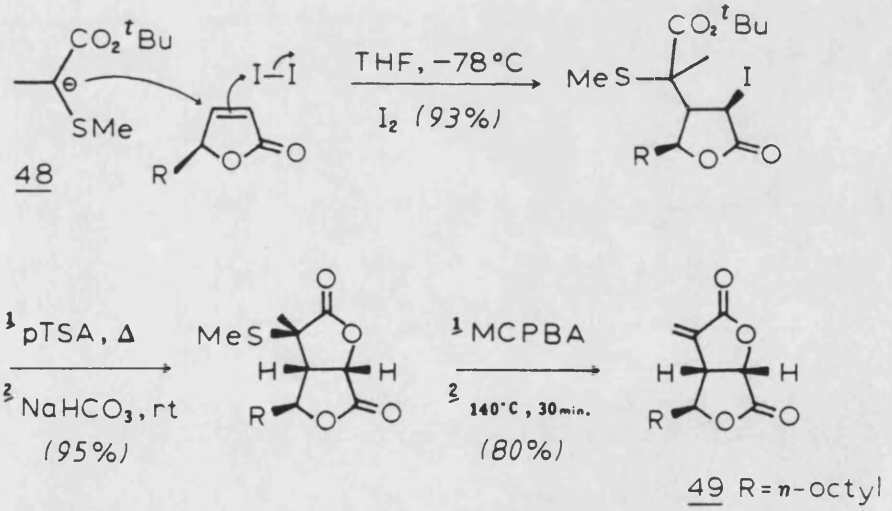
and reaction of the stable anion 45 with primary alkyl iodides or allyl bromides gives the α-substituted Mannich bases[43] 46. The deprotection sequence begins with a quantitative quaternisation of the amine nitrogen with iodomethane, subsequently followed by treatment of the ammonium salt in refluxing benzene, with the Eiter base,[44] DBN, to afford the acrylates 47 in 74-87% isolated yield (Scheme 19).



Scheme 19

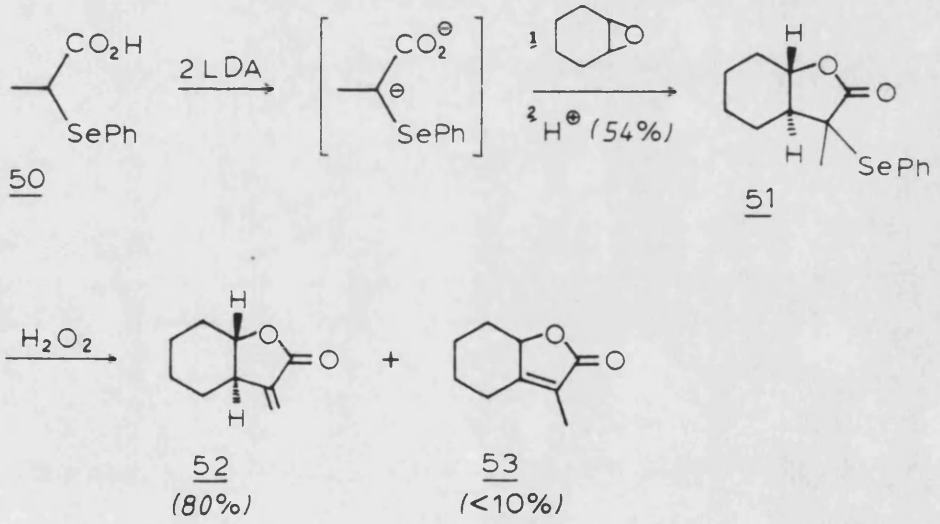
Helquist reported[40a] that 45 was not sufficiently nucleophilic to give good yields with other, less reactive alkyl halides, and epoxides, even when the potassium enolate was employed.

Schlessinger *et al.*[45] used the mono-anion of *t*-butyl 2-(methylthio)propionate 48 to introduce a masked acrylate d^2 reagent to the β- position of a butenolide in a conjugate addition-halogenation sequence,[46] leading to the novel, fungicidal bislactone *dl*-avenaciolide[47] 49. The addend and receptor combination was then employed to construct the α-methylene-γ-butyrolactone ring[48] by a sequence involving iodolactonisation, and thermal elimination of the sulphoxide (Scheme 20).



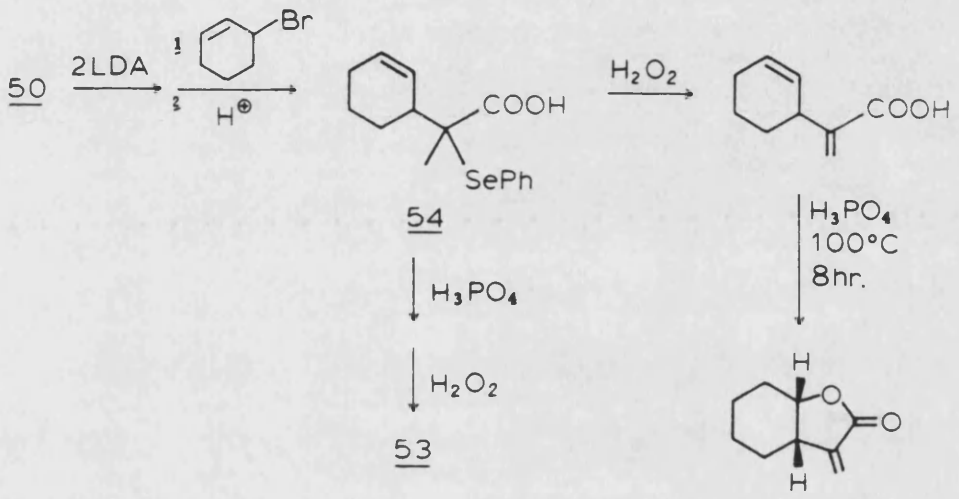
Scheme 20

2-Phenylselenopropionic acid 50, prepared from sodium phenylselenate and sodium 2-bromopropionate,[49] was doubly metallated by Petragnani and Ferraz,[50] and used for the construction of α-methylene-γ-butyrolactones.[51a] After cyclisation, the double bond can be regenerated by elimination of the selenide, which only needs to be oxidised to the selenoxide.[51c] Intramolecular elimination from 51 is spontaneous, and the *trans*-lactone 52 is formed (Scheme 21), as the major product.



Scheme 21

Alternatively, the formation of *cis*-lactone 55 *via* the γ,δ-unsaturated acid 54 depends on the correct oxidation/elimination-lactonisation sequence. However, if acid-lactonisation precedes selenoxide elimination, 53 is obtained as the major product (Scheme 22).



Scheme 22

This approach is reported to complement and extend previously published methods in which selenenyl[52] or sulphenyl[53] groups are introduced into preformed lactones.

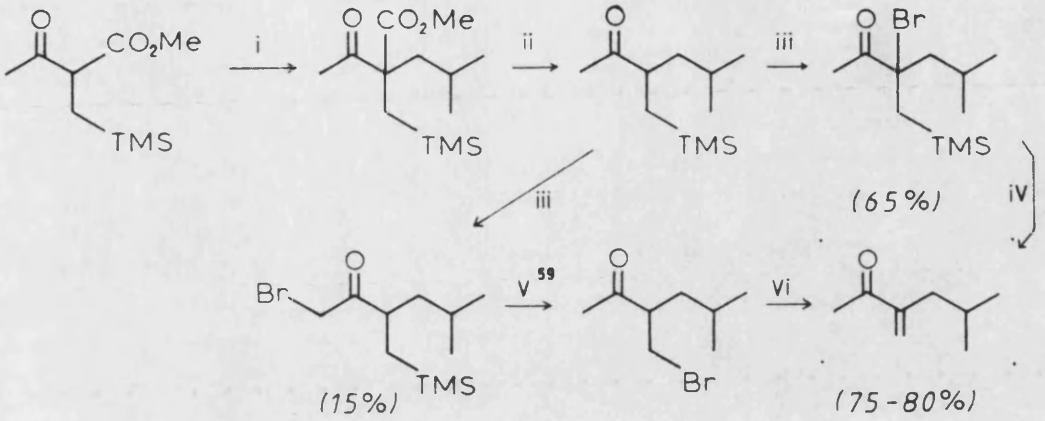
The lactonisation of unsaturated acids leading to *cis*-fused α-methylene lactones depicted in Scheme 22 is reported to be simpler than that involving vinylcuprate reagents.[34a]

Fleming *et al.*[54] accomplished the masking of the double bond by introducing a trimethylsilyl group. The idea that a β-trimethylsilyl propanone could serve as a masked form of the α,β-unsaturated system was present in the work of Eberson,[55] but was not developed. What made this methodology particularly attractive was the fact that β-halogeno, -hydroxy, or -aminoketones undergo

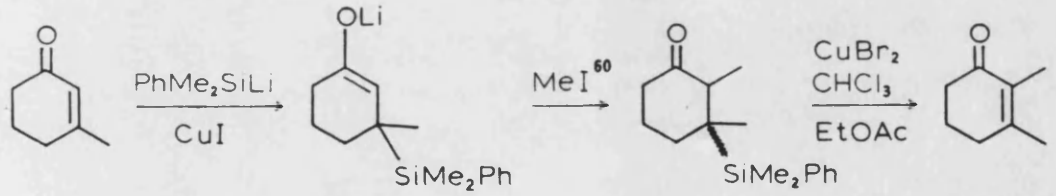
elimination with base, whereas β-trimethylsilyl will not, being stable to most reagents commonly used in organic synthesis. In addition, building on Still's[56] observation, Fleming found that Me_3SiLi,[57] or the more easily prepared $PhMe_2SiLi$,[58] add conjugatively to α,β- unsaturated ketones, aldehydes, and esters in the presence of copper (I) iodide at -23 °C (a higher temperature than that reported by Still). Elimination of the silicon group is effected either by a bromination,[54b] or by use of cupric bromide[54c] for cyclic ketones (Scheme 23).

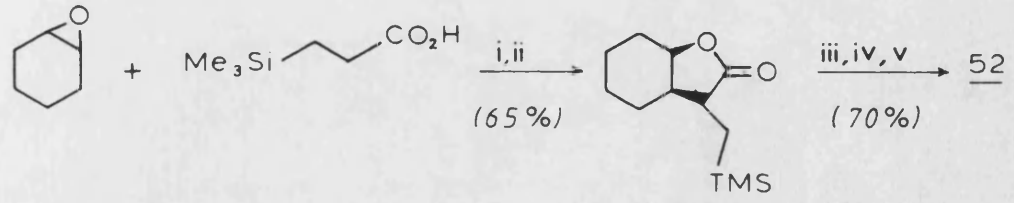
Raucher *et al.*[61] used the β-phenylseleno ortho ester 56 as a synthon for the preparation of (methyl) α- substituted acrylates *via* the Claisen ortho ester rearrangement[62] with allylic alcohols followed by β- elimination of the selenium group (Scheme 24). However, the above procedure was limited by the thermal stability of 56 which undergoes rapid decomposition at temperatures greater than 170 °C. A year later, therefore, the β-methoxy derivative 57 appeared in the literature.[63] 57, available in 72% yield from 3-methoxypropionitrile by a Pinner[64] reaction, was thermally stable at its atmospheric boiling point (185 °C) for longer than 48 hours (Scheme 25).

By analogy with Raucher's synthesis,[61] Still *et al.*[65] started from an allylic alcohol, and used the methylenic variant of the Claisen rearrangement, *i.e.*, the Ireland variant, for the regio- and stereo-specific introduction of intact or masked acrylic acid residues (Scheme 26).



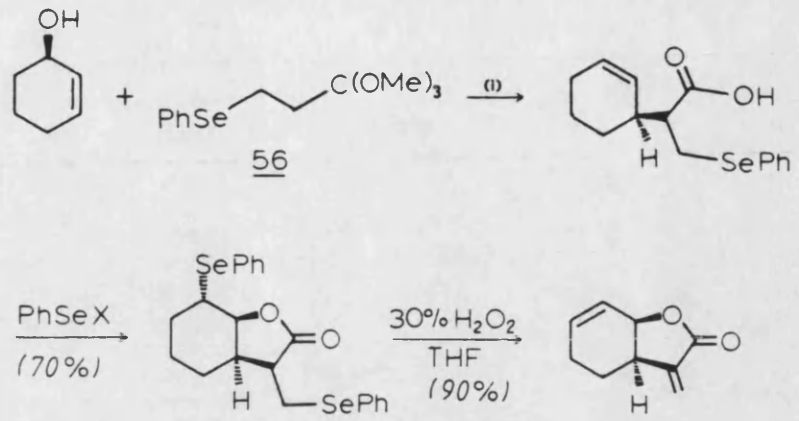
(i) NaH, DMF, ^{i}BuI; (ii) NaCN-HMPA, 90°C; (iii) Br_2, CCl_4; (iv) NaF, EtOH; (v) HBr, CCl_4; (vi) $NaHCO_3$, EtOH, H_2O.



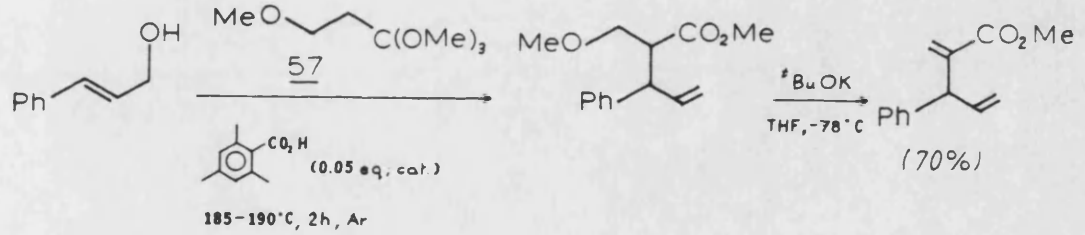


(i) 2 LDA, 0°C then Δ; (ii) TsOH, $PhCH_3$, Δ; (iii) LDA, THF, −78°C; (iv) Br_2, CCl_4, −78°C; (v) $(PhCH_2)N^{\oplus}Me_3F^{\ominus}$, THF.

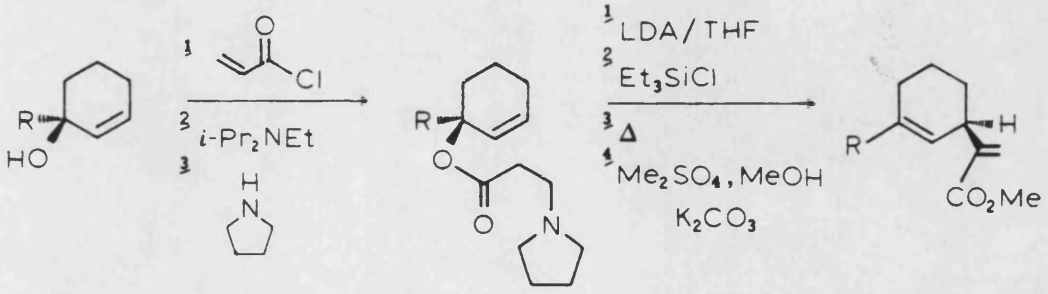
Scheme 23



Scheme 24. (i) *a*) heating in mesitylene (160°C, 24h) in presence of Me_3CCO_2H (0.1eq.); *b*) demethylation with LiI in 2,6-dimethylpyridine, Δ, 2h.

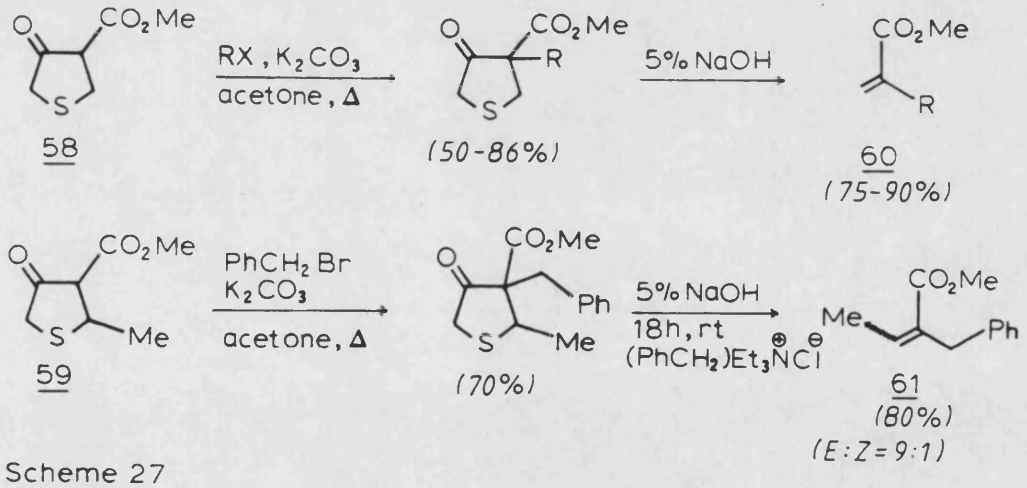


Scheme 25



Scheme 26

The α-functionalisation of acrylate and crotonate esters was undertaken by Pollini *et al.*,[66] the problem of proton abstraction from C-2 of crotonates having been mentioned previously (page 6). The piperidine-catalysed Michael addition of methyl thioglycolate to methyl acrylate and methyl crotonate, followed by Dieckmann cyclisation of the adducts afforded methyl 4-oxothiolane-3-carboxylate[67] 58, and its 2-methyl derivative 59, respectively. Alkylation under mildly basic conditions was followed by a tandem of retrograde Dieckmann-Michael reactions, with sulphur acting as the leaving group (Scheme 27), to yield the products 60 and 61 in the yields shown below.



58 (50-86%) 60 (75-90%)

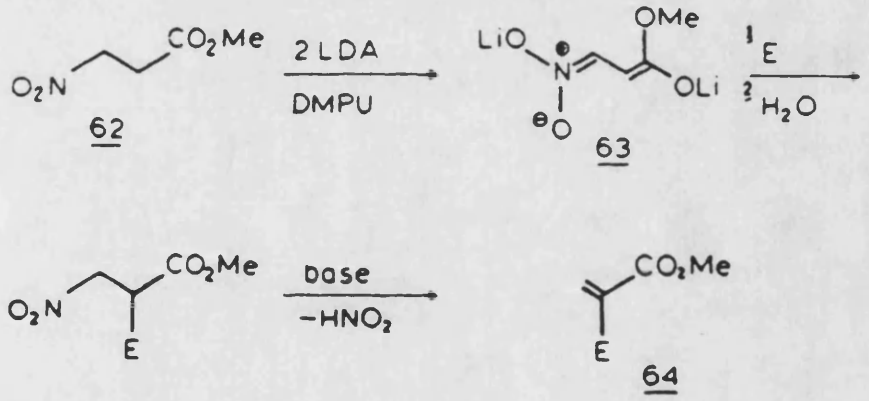
59 (70%) 61 (80%) (E:Z = 9:1)

Scheme 27

Although *O*-alkylation was a minor problem, the above sequences represented efficient preparation of α-substituted acrylic esters. However, the methodology could not be applied to the synthesis of

α-methylene lactones because less reactive alkylating agents such as epoxides, failed to react.

Seebach *et al.*[68] offered an alternative to the general methods described at the beginning of this section. Methyl 3-nitropropanoate 62 was doubly deprotonated with LDA in the presence of HMPA, or preferably the cyclic urea DMPU,[69] at the α-nitro and α-carbonyl positions. The dianion 63 could be alkylated or hydroxyalkylated by alkyl halides and aldehydes, and base-elimination of nitrous acid afforded acrylates 64 (Scheme 28).

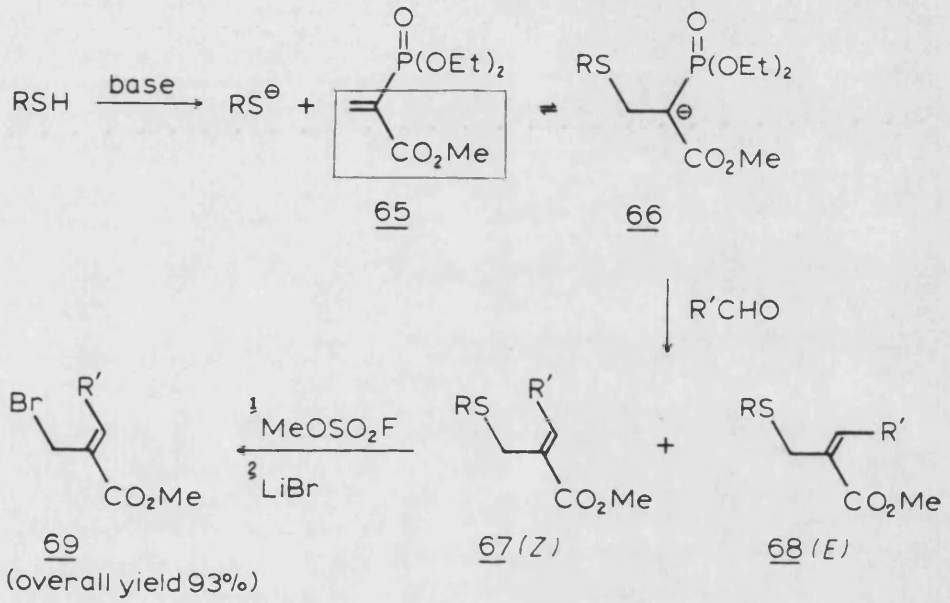


Scheme 28

Good yields were obtained in reactions of 63 with primary and secondary alkyl iodides, allyl and benzyl bromide. However, a Michael adduct was formed with cyclohexenone, and although poor yields were obtained with acetone and cyclohexanone, there was no reaction with oxirane.

The allylic sulphur compound 67, used by Semmelhack *et al.*[70] in the synthesis of α-methylene-γ-lactones, was prepared by a method based on Wittig chemistry. The initial step from methyl 2-(diethylphosphono)acrylate[71] 65 simultaneously masks the double bond, and

creates the reactive site. Subsequent reaction with aldehydes affords the geometric isomers 67 in high yield, but relocating the double bond. The reaction can be made (Z)- selective by choosing the appropriate thiol and base (Scheme 29).

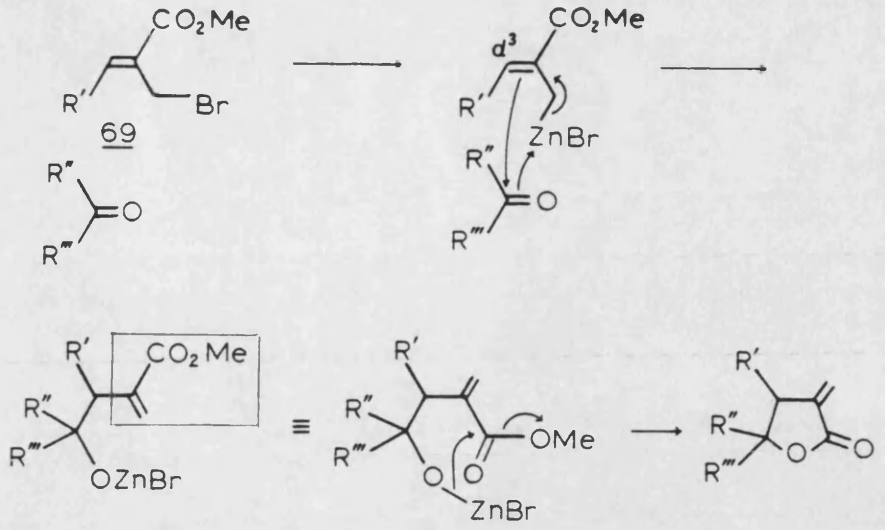


(overall yield 93%)

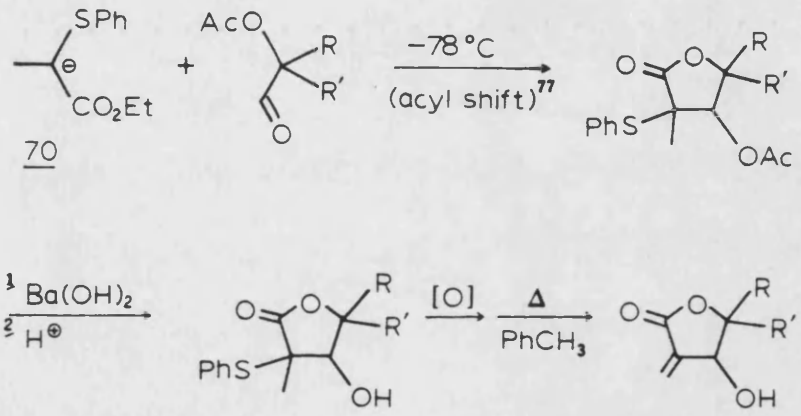
Scheme 29. When R = isopropyl, base = *n*-BuLi/THF, (Z):(E) = 9:1.

The original double bond is only revealed when 69 was employed in the Dreiding-Schmidt[72] reaction in which a (Z)-2-bromomethyl-2-alkenoic ester[73] 69 is treated with zinc to give a d^3 intermediate with umpolung (Scheme 30).

In a similar way to both Schlessinger *et al.*[45] and Petragnani,[50] Benezra *et al.*[74] used the mono-anion of ethyl 2-(phenylthio)propionate 70 as a d^2 acrylic acid synthon.[75] The sulphide group can be removed after oxidation to the sulphoxide, requiring heating for elimination to occur[76] (Scheme 31).



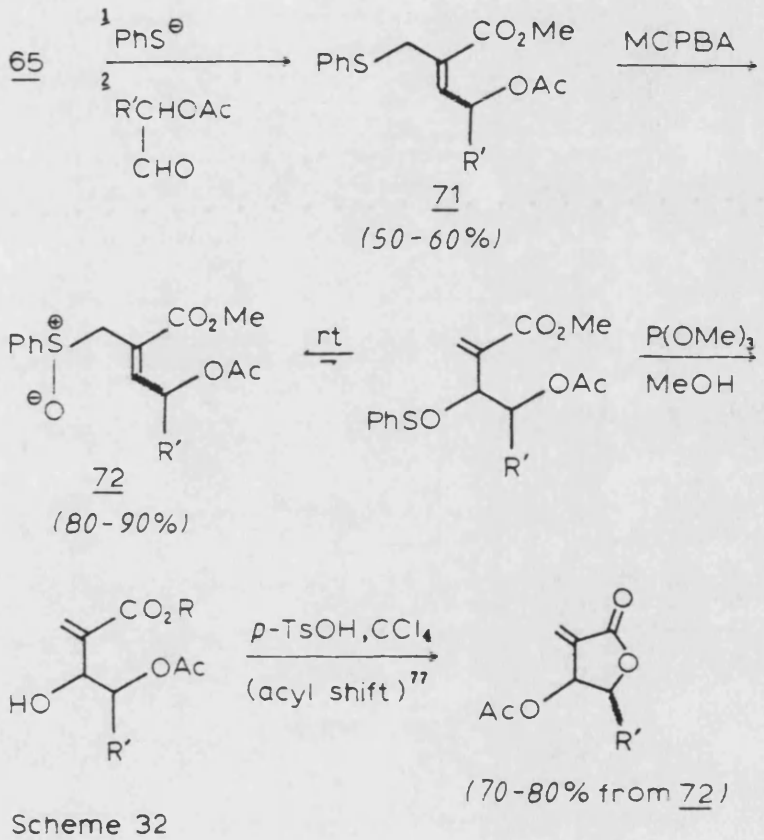
Scheme 30



Scheme 31

A strategy that combines elements of both Semmelhack's[70] and Benezra's[74] work, is shown in Scheme 32.[78] 1,4-Addition of phenylthiolate to the Semmelhack (diethylphosphono)acrylate[79] 65 followed by oxidation of the adducts 71 affords the sulphoxides 72. The original double bond is exposed in a sulphoxide-sulphenate rearrangement,[80] the use of trimethyl phosphite as a thiophilic reagent helping to displace the equilibrium in the desired direction.

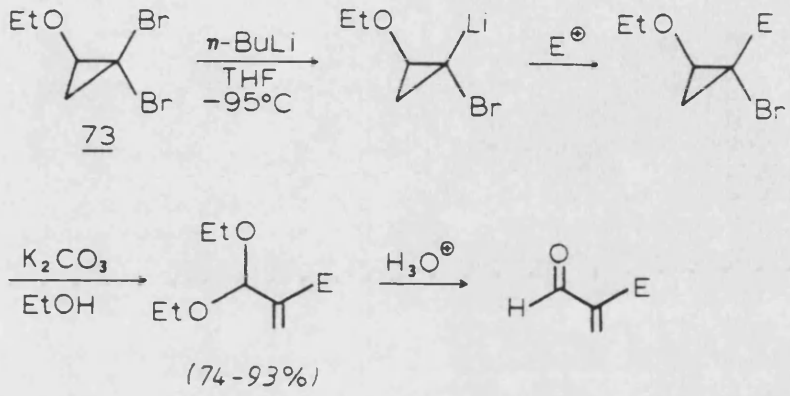
Hiyama *et al.*[81] used the unsymmetrical alkoxycyclopropane 73 as a synthetic equivalent of 2-lithiopropenal. Prepared from ethyl vinyl ether and dibromocarbene, the adduct 73 is subjected to halogen-metal exchange conditions and alkylated. The potential ambident reactivity of the cyclopropanol derivative is controlled by a specific ring opening operation. In this case, therefore,



Scheme 32

instead of acting as a d^3 homoenolate anion equivalent (see Section 1.2.3.1), the electrophile is located at C-2 (Scheme 33).

The problem of C-2 alkylation of 2-alkenoic esters having substituents at C-4, tackled previously by Pollini *et al.*,[66] was investigated by Sato *et al.*[82] The reaction of the lithium enolate derived from *t*-butyl 2,2-bis(trimethylsilyl)acetate 74 with straight-chain aliphatic aldehydes affords α-silylcrotonate ester derivatives[83] 75. If 75 are subjected to fluoride-induced



73

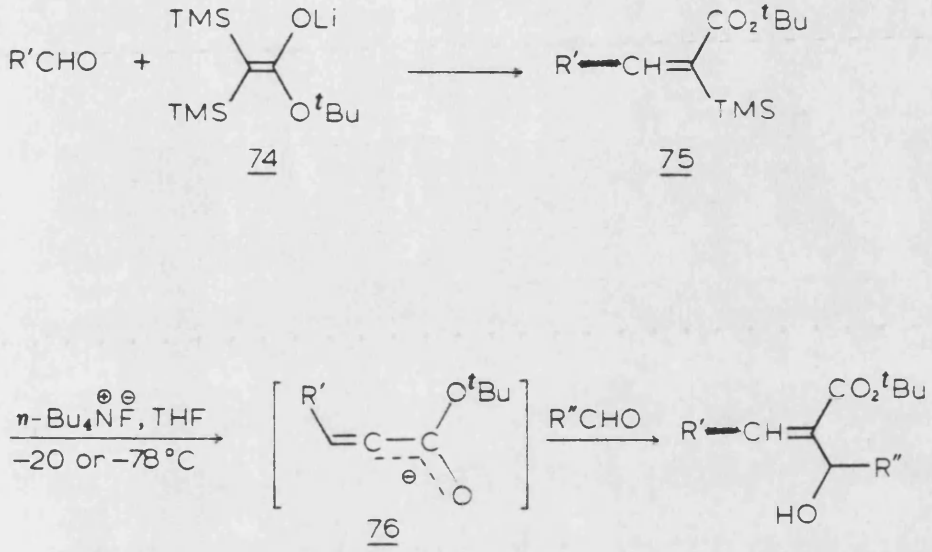
(74-93%)

Scheme 33. E = Br, $SiMe_3$, SPh.

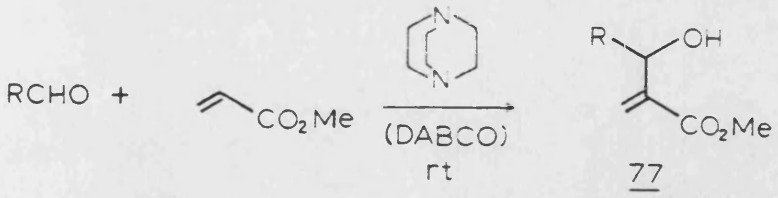
desilylation, the anionic centre is regioselectively generated at the α-C atom through the intermediacy of an allenoate unit[84] 76. Reaction with aldehydes affords β-hydroxy esters in 66-90% yield (Scheme 34), but both (Z)- and (E)-isomers are formed.

It has been known for some time that acrylic acid derivatives could be coupled to a range of aldehydes in high yields using bicyclic tertiary amine catalysts.[85] Since then, Hoffmann *et al.*[86] have used this methodology in the synthesis of a wide range of allyl alcohols by DABCO (1,4-diazabicyclo[2.2.2]octane)-catalysed coupling of acrylic esters and aldehydes, to give 77. The amine is involved in the first step of the catalytic cycle: conjugate addition to the acrylate (Scheme 35).

So far, only aldehydes have been examined in detail, but Perlmutter *et al.*[87] found that analogous systems, tosylimines of

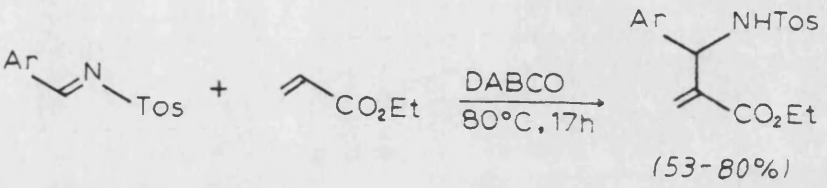


Scheme 34 . R'= n-alkyl .



Scheme 35

aromatic aldehydes[88] for example, react well under similar conditions (Scheme 36).

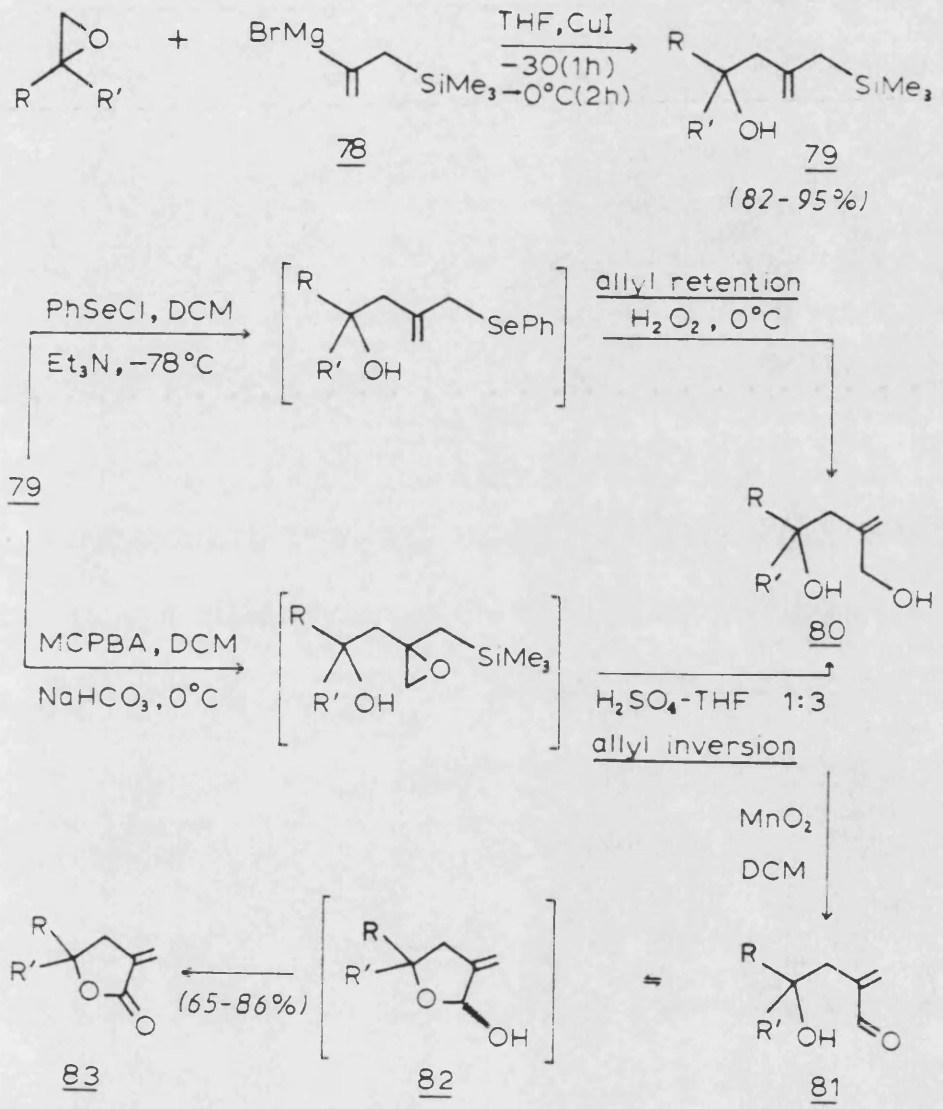


Scheme 36

The reaction is, however, only really useful for acrylates themselves; no β- substitution can be tolerated as the reaction fails for β- substituted acrylates.[87]

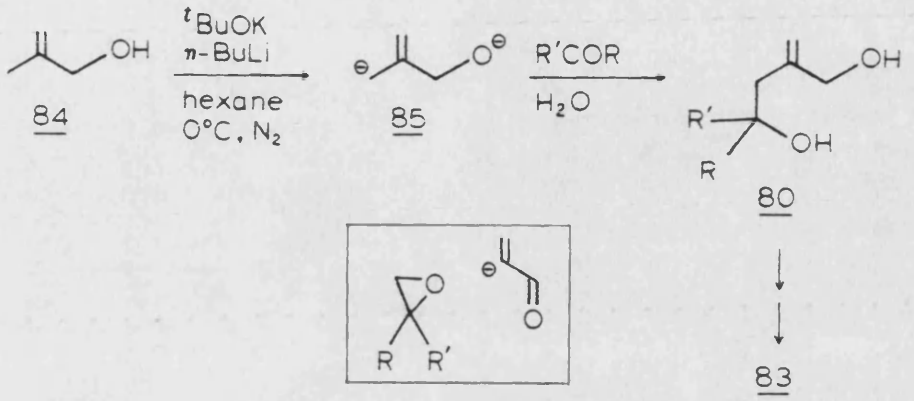
The allylsilane 78 was employed by Itoh *et al.*[89] as a masked d^2 acrylic acid.[90] Strictly speaking, 2-bromoallyltrimethylsilane[91] served as the synthetically useful (1-hydroxymethyl)vinyl anion[92] (see *C*, page 7). Grignard reagent 78 was readily introduced to epoxides to give 2-(2-hydroxyethyl)allylsilanes 79. The allyl alcohols 80 were obtained by either of the desilylating oxidative routes shown (Scheme 37) and oxidised with active MnO_2 to give selectively the α,β- unsaturated aldehydes. *In situ* oxidation of the hemiacetals 82 afforded lactones 83 in 65-86% yield.

Carlson *et al.*[93] had also previously employed the route from 80 to 83, but had started with a four-carbon unit, 2-methylprop-2-en-1-ol 84, as a synthetic equivalent of the methacrylic acid dianion. The strongly basic Schlosser combination of potassium *t*-butoxide and *n*-butyl lithium[93] was used to form the alkoxide and simultaneously deprotonate the weakly acidic allyl position. Treatment of 85 with carbonyl compounds resulted in C-alkylation to give 80, but low to



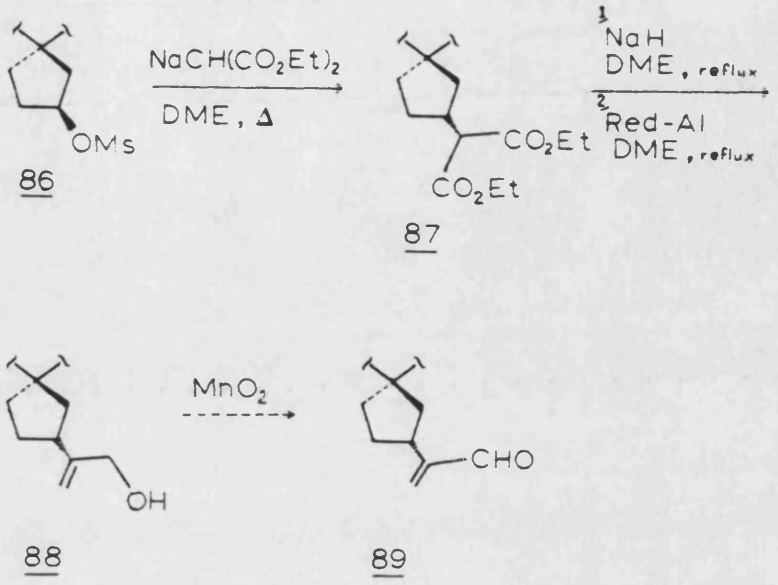
Scheme 37

moderate yields were reported for the addition step (Scheme 38).



Scheme 38. This d^2 synthetically equivalent reaction sequence can be regarded as the formal addition of α-lithioacrolein to an epoxide.

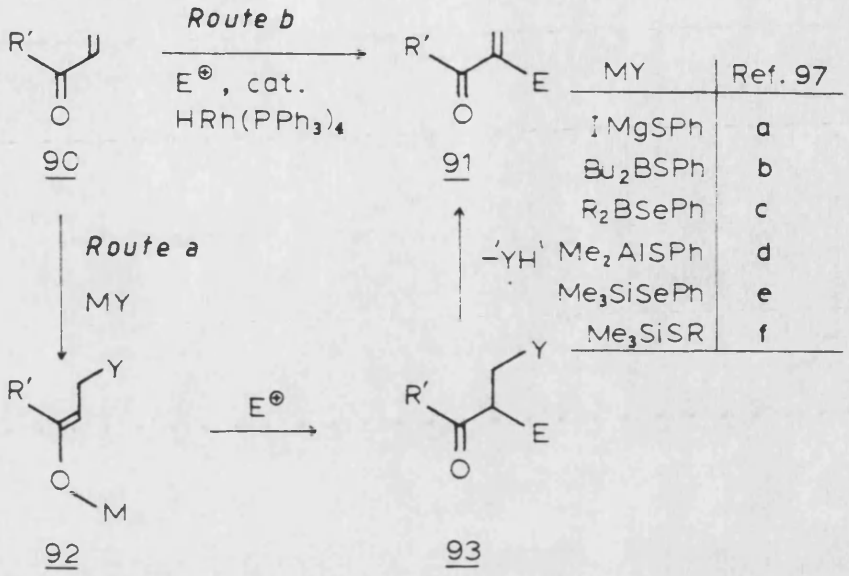
It is known that enolisable 1,3-dicarbonyl compounds frequently afford products of reduction and elimination on treatment with lithium aluminium hydride.[94] Iwata *et al.*[95] in an approach to a phytoalexin natural product, appended an allylic alcohol from C-2 using a procedure which began by reaction of the mesylate 86 with the anion of diethyl malonate to give 87. Transformation of the bis(ethoxycarbonyl)methyl group to the 1-(hydroxymethyl)vinyl one was efficiently achieved by a modification of a known method.[96] The sodium salt of 87 was reduced with a large excess of Red-Al in boiling DME to afford the expected 88 (Scheme 39). Although the hydroxyl group was removed in Iwata's approach, one can envisage a mild oxidation of 88 with MnO_2 affording the α- substituted acrolein 89.



86 87 88 89

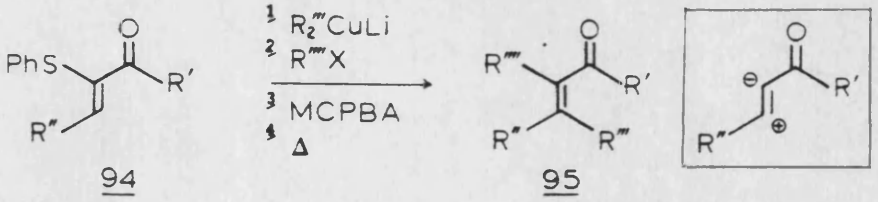
Scheme 39 . Red-Al= $(MeOCH_2CH_2O)_2AlH_2$.

There have been several attractive approaches for the introduction of electrophiles to the α- position of enones based on the common procedure outlined in Route a[54c,97] (Scheme 40). The strategy involves use of an equimolar amount of MY conjugatively added to the enone 90 followed by attack of the electrophile and elimination of "H-Y" from 93 to afford 91. Recently the direct approach of Route b has been realised by Matsuda *et al.*[98] exploiting a catalytic cycle with a rhodium complex, and applied to aldol type carbon-carbon bond formation.



Scheme 40

Warren *et al.*[99] employed a similar approach, but using an enone 94 already incorporating a leaving group at the α- position. The normal good acceptor property of 94[100] resulted in conjugate addition of the cuprate and introduction of an α- substituent. Oxidation and elimination of the phenylthio group regenerates the double bond (Scheme 41).

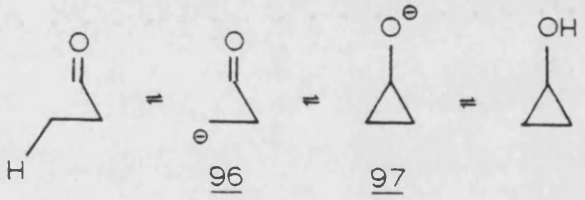


Scheme 41

1.2.3 Homoenolate Anion Reagents and Related Species

1.2.3.1 Introduction

Although enolisation is an established phenomenon, the recognition of homoenolisation, as portrayed in Scheme 42, is a relatively recent event.

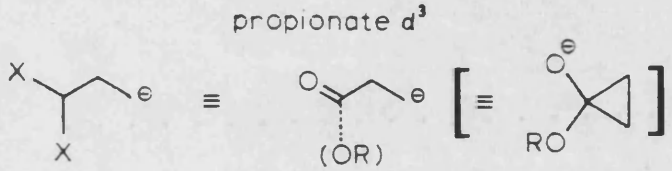


Scheme 42

This is a direct consequence of wanting to design a donor centre at what is normally an acceptor reactive site. In the case of enones, although Michael-type nucleophilic addition is well-known, it means that the β-carbon atom of the system can only act as an electrophile, never as a nucleophile. The concept of homoenolisation, therefore, as in the design of acyl d^1 reagents, has become one of the major topics with respect to polarity inversion[101] or umpolung.[102] Because vigorous conditions are required to generate even low concentrations of homoenolates, and because the homoenolate anion 97 itself does not normally show nucleophilic reactivities toward carbon electrophiles,[103] the problem has been overcome through the development of a variety of synthetically equivalent reagents; most of which structurally resemble the open form of homoenolates 96, or the related acrylic species.[102b,104]

Although a variety of approaches have been used, all the previous simple equivalents fall into three classes:

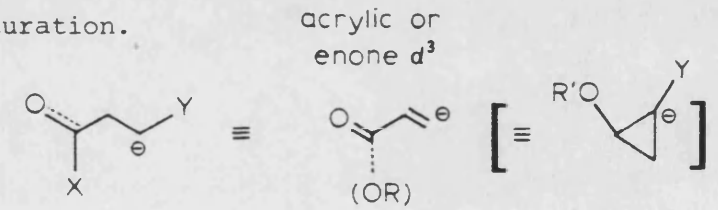
1a) This category includes systems possessing a single nucleophilic site β to a masked carbonyl group, and in some cases the anion is stabilised by a substituent at the β- site.



masked ketone or aldehyde

masked acid or ester

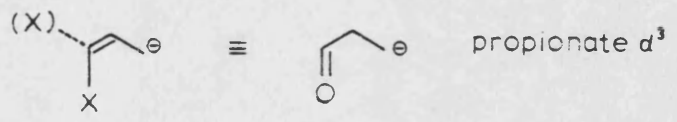
b) In the case of acrylic compounds, the normal Michael addition can be employed to introduce this β- group, and the acyl group is then protected by acetalisation or ketalisation. The β-masking group is removed after the desired synthetic step to reveal the α,β- unsaturation.



masked acid, ester, ketone, or aldehyde

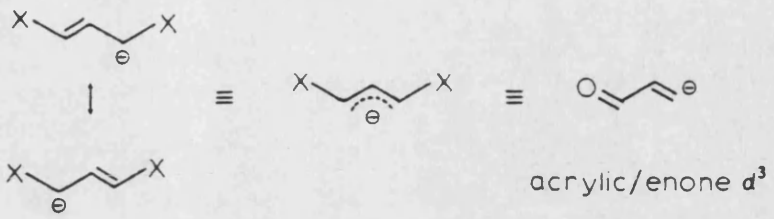
masked aldehyde

2a) Attempts can also be made to control the ambident nucleophilicity of heteroatomically stabilised/substituted allylic anions to overcome the frequently encountered problem of positional isomers (α-alkylation).



b) In this category, provision has to be made for introducing the double bond if β- substituted acrylic compounds are desired.

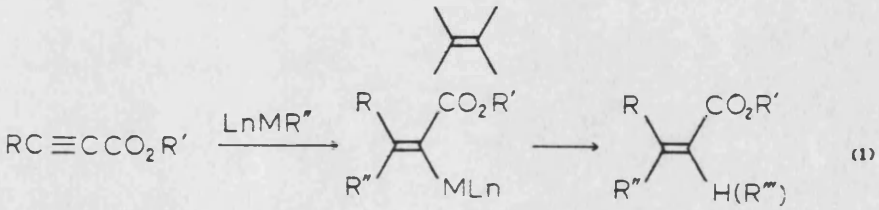
This simplifies the site selectivity problem with the use of a symmetrical anion.



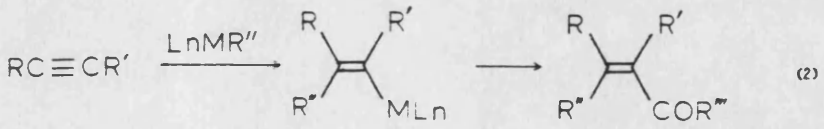
3. As in the construction of d^2 acrylic compounds, there are also several methods which employ allenes and acetylenes in the design of acrylate d^3 reagents.

Functionally substituted alkynes have been used as acrylate d^3 synthons in two general ways:

a) Organometallic reagents are added regioselectively across acetylenic carboxylates, and mono- or di-substituted acetylenes. The appended organometallic moiety can be used further, either to introduce new vinyl substituents (equation 1), or in the latter case to introduce the carbonyl group itself, directly or *via* precursors (equation 2).



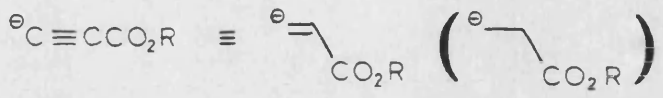
(1)



(2)

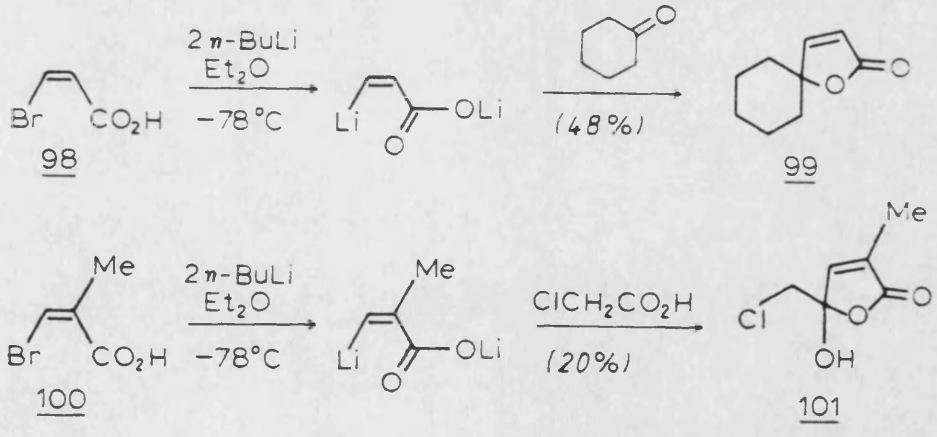
b) Alkylation of α,β-alkynyl carboxylates, exploiting the acidity of the C_{sp}-H group, is followed by partial reduction of the triple

bond to give either (Z)- or (E)-β- substituted acrylates. Alternatively, the formation of the carbon-carbon double bond is accomplished by addition of an organometallic reagent, simultaneously creating the possibility of further functionalisation.



1.2.3.2 Acrylate Anion d^3 Reagents

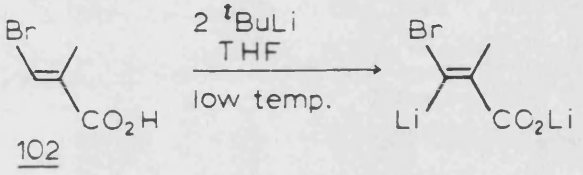
In synthesising various γ- substituted α,β-butenolides, Caine *et al*.[105] found that the acid function of acrylic derivatives is well enough protected if it is simply present as the carboxylate anion.[106] Treatment of (Z)-3-bromopropenoic acid[107] 98, or the α-methyl derivative[108] 100 with butyl lithium, and reaction with carbonyl compounds afforded butenolides in poor to moderate yields (Scheme 43).



Scheme 43. 99 = 1-Oxaspiro[4.5]dec-3-ene-2-one[109]
101 = Lepiochlorin[105c,133]

Although formation of acetylenic carboxylates remained an unsolved problem for 98, increased yields could be obtained by incorporating a β-bromo- substitutent in 98 and 100 to reduce basicity, and increase the nucleophilicity of the dilithio species.

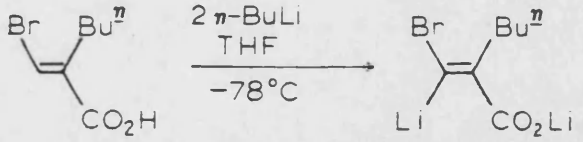
It had been reported[110] that the β-bromo acrylic derivative 102 could be converted into the β,*O*-dianion using the relatively more basic *t*-butyl lithium reagent (Scheme 44). Caine *et al.*[105e] used



102

Scheme 44

similar methodology in generating the lithium (Z)-β-bromoacrylate derivative 103 (Scheme 45).

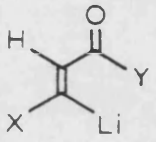


103

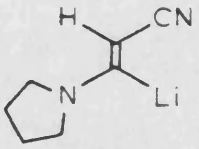
Scheme 45

The possibility of co-ordination of the $C_\beta^-Li^+$ bond by an ester group is not sufficient to promote direct deprotonation of the C_β-H bond of methyl acrylate, unless its acidity is being increased by substituents at C_β.[13b] Schmidt *et al.*,[111] investigating β-functionally substituted acrylic compounds, have demonstrated that

these compounds are accessible to direct C-lithiation without previous protection of the carboxylic functionality. The generation of stable vinyl lithium derivatives is temperature dependent, and below -100 °C prevails over the expected 1,2- or 1,4- addition of the lithiating agent to acrylate systems. The regioselectivity of lithiation is mainly determined by β-alkoxy-, β-dialkylamino-, and β-alkyl/aryl mercapto groups on the one side, and the carboxylic ester or amide functionality on the other side (Scheme 46, compounds 104).



104



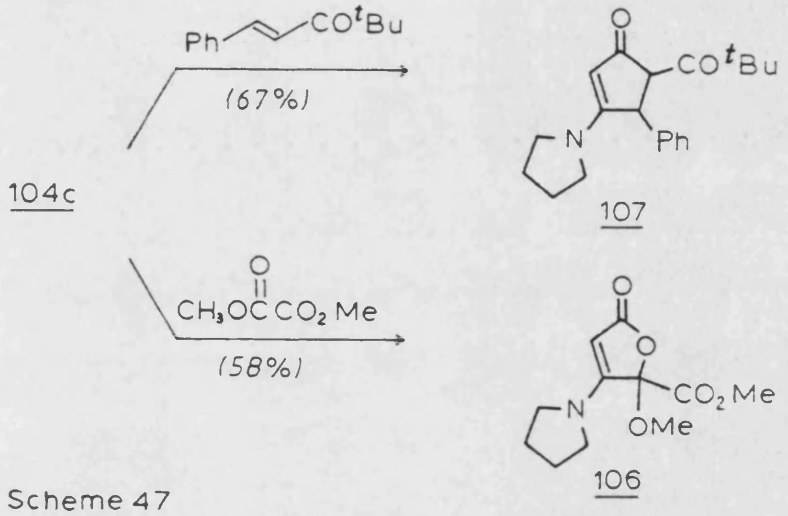
105

104	X	Y	Refs.
a	Ph	OEt	13b
b	RO	OR	111e
c		OEt	111d,e
d		NEt_2	111a,e
e	PhS	OLi	111g,e
f	EtS	OLi	111e,f

Scheme 46. R=Alkyl

In addition, some acrylic acid derivatives 105[111a,b,e] can be lithiated selectively in either the α- or β- positions by use of kinetic or thermodynamic control.

The presence of an unprotected electrophilic carboxylic group allows for interesting ring closure reactions leading to butenolides 106,[111c,d] tetronates, cyclopentenones 107, and derivatives which are portions of many natural products[111e] (Scheme 47).

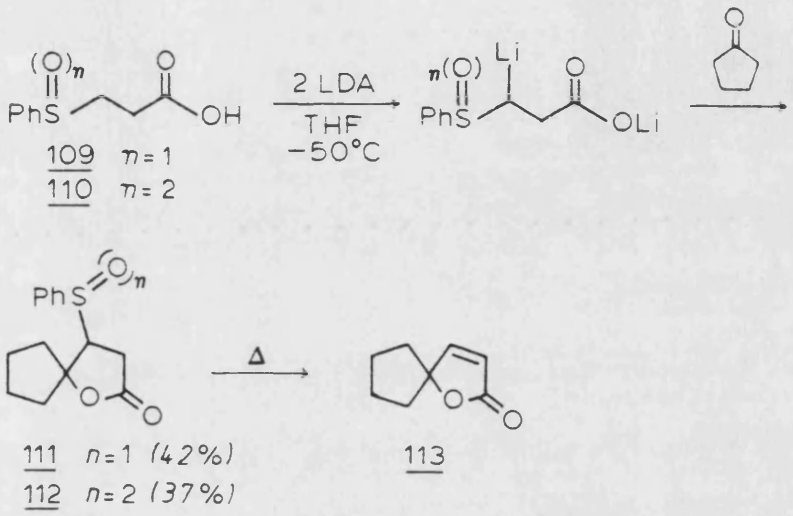


Scheme 47

Uda *et al.*[112] found that dianions could be prepared from 3-phenylsulphinyl- and 3-phenylsulphonyl-propionic acids 109 and 110, and reacted with cyclopentanone to afford dihydro-2(3H)-furanones 111 and 112 in 42% and 37% yield respectively. These could be transformed by pyrolysis to the butenolide[113] 113 (Scheme 48). In contrast, 3-(phenylthio)propionic acid[114] 108, from which 109 and 110 were easily prepared, did not react to form the 3-carbanion; rather, elimination of the phenylthio group took place.

Tanaka *et al.*[115] used the dianion of the β-sulphonylpropanamide 114 in a similar manner.[116] Alkylation with aldehydes and ketones afforded γ-hydroxyamides 115 which were employed for the construction of 5-alkyl-2(5H)-furanones 116 in 54-80% yields (Scheme 49). The use of an amide instead of the acid 110, allowed for the incorporation of a chiral *N*-alkyl residue; and resulted in high yields of

optically pure butenolides 116 as a direct consequence of being able to separate the diastereomeric γ-hydroxy amides prior to cyclisation and elimination.

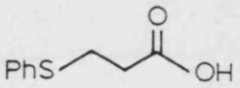


109 n=1
110 n=2

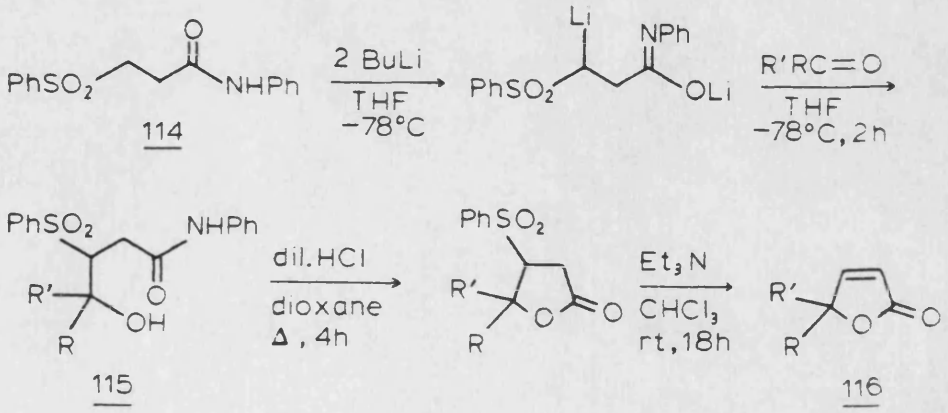
111 n=1 (42%)
112 n=2 (37%)

113

Scheme 48



108



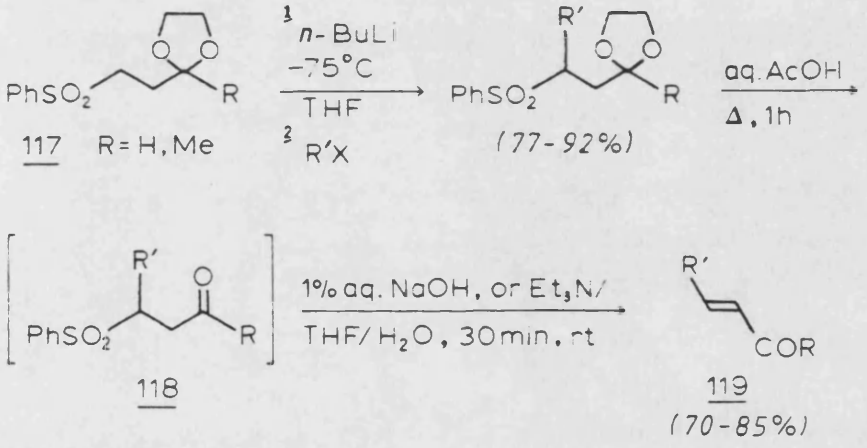
114

115

116

Scheme 49

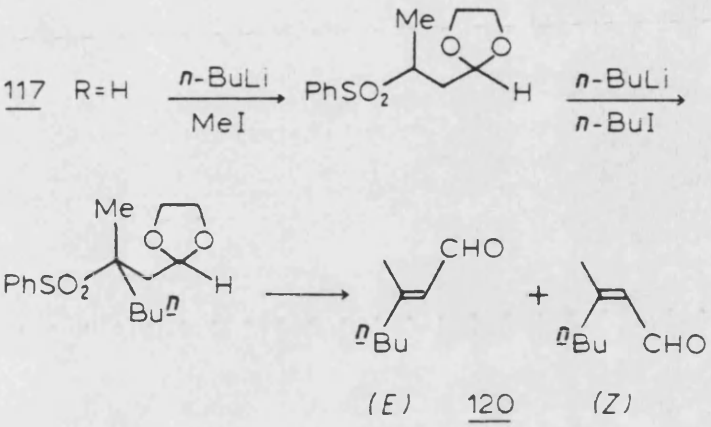
Kondo *et al.*[117a] used the normal acceptor reactivity of the β-carbon atom to introduce the phenylsulphonyl moiety to acrolein and methyl vinyl ketone *via* 1,4- addition. The dioxolane derivative[118] 117 was subsequently metallated and alkylated, and removal of the acetal/ketal protecting group afforded the carbonyl compounds 118. The sulphone masking group was eliminated under mild conditions to afford enones 119 in 70-85% yields with (E)-selectivity (Scheme 50).



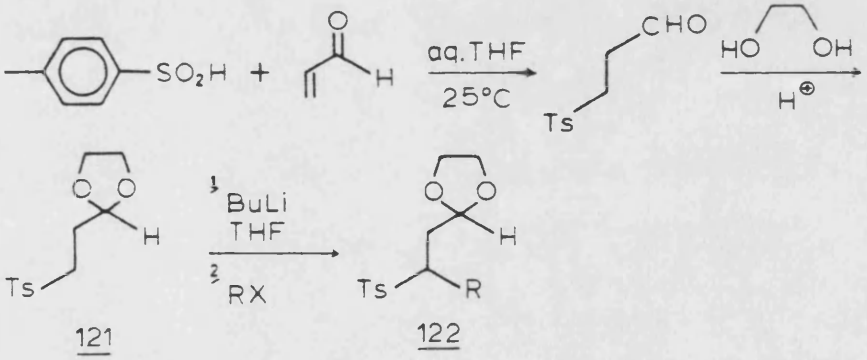
Scheme 50

By employing a consecutive alkylation sequence, this methodology also provided β- substituted crotonaldehyde derivatives[119] 120, thus avoiding the vinyl *versus* allyl problem mentioned in Section 1.2.2 (Scheme 51).

Dolby *et al.*[120] used a similar approach to that of Kondo, appending instead a *p*-toluenesulphonyl group to the β- position of acrolein affording 3-(*p*-toluenesulphonyl)propanal. After protection of the carbonyl functionality, α-sulphonyl carbanions could be generated and utilised as shown previously (Scheme 52).

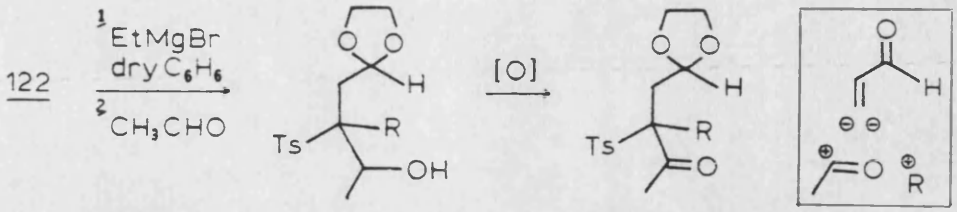


Scheme 51. *(E):(Z)=67:33*.



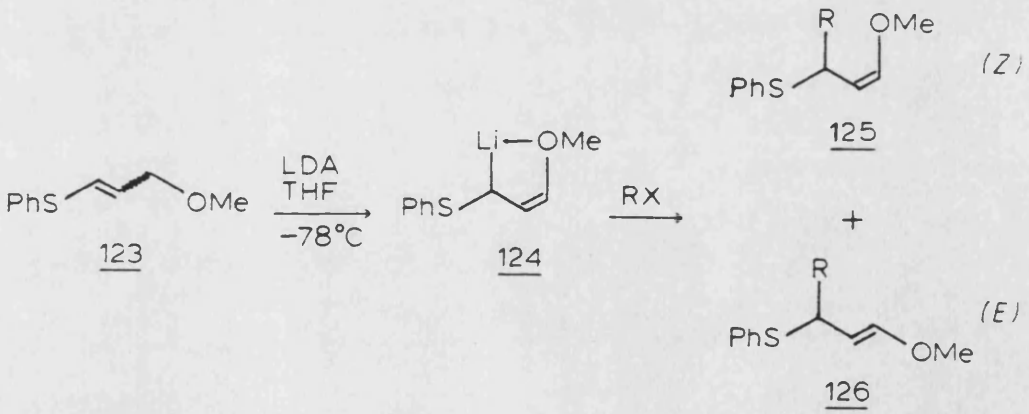
Scheme 52

Reaction of the carbanions derived from 121 and 122 with acylating agents gave low (<50%) conversions,[117a,121] and could only be accomplished indirectly using the magnesium carbanions and a hydroxyethylation-oxidation sequence. The alternative method involving a formal acylation followed by alkylation, gave largely *O*-alkylation (Scheme 53).



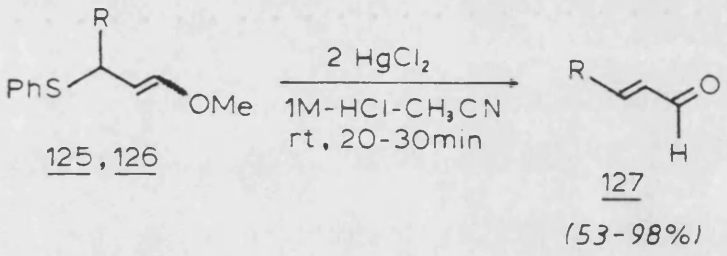
Scheme 53

Taguchi *et al.*[122a] found that 3-methoxy-1-(phenylthio)prop-1-ene[122b] 123, prepared from thiophenol and 3-chloro-1,2-epoxypropane (epichlorohydrin) served as a useful β-formyl vinyl anion equivalent.[122c] Reaction of the geometric isomers 123 with LDA was followed by exclusive alkylation at the α-phenylthio position, relocating the double bond to form an enol ether at the same time (Scheme 54).



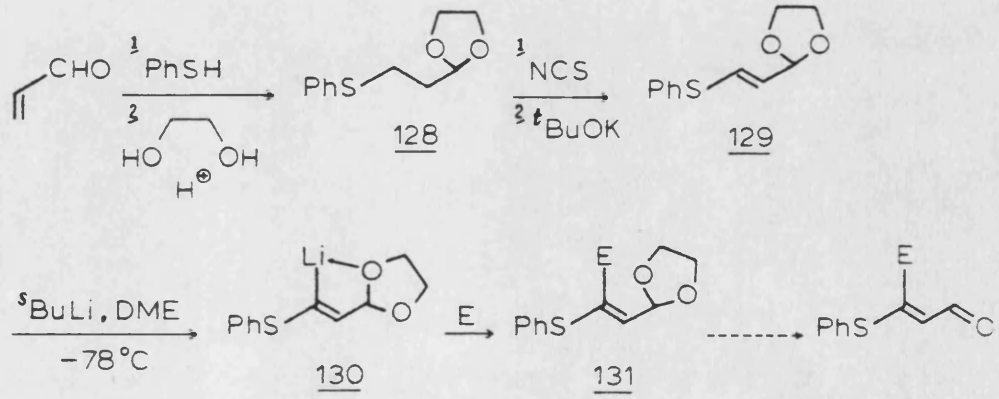
Scheme 54. RX = primary alkyl halides, alkyl tosylates, allyl bromides allyl chlorides. When RX is 1-bromo-2-phenylethane, *(Z):(E) = 9:1.*

Formation of the (Z)-isomer 125 always predominated over the formation of the (E)-isomer 126 (usually ~2-3:1), probably because the most stable lithiated species was that in which chelation maintained a (Z)- configuration. 125 and 126 could both be subsequently converted to (E)-β- substituted acrolein derivatives 127 in 53-98% yields using thiophilic mercuric ion under mild conditions (Scheme 55).



Scheme 55

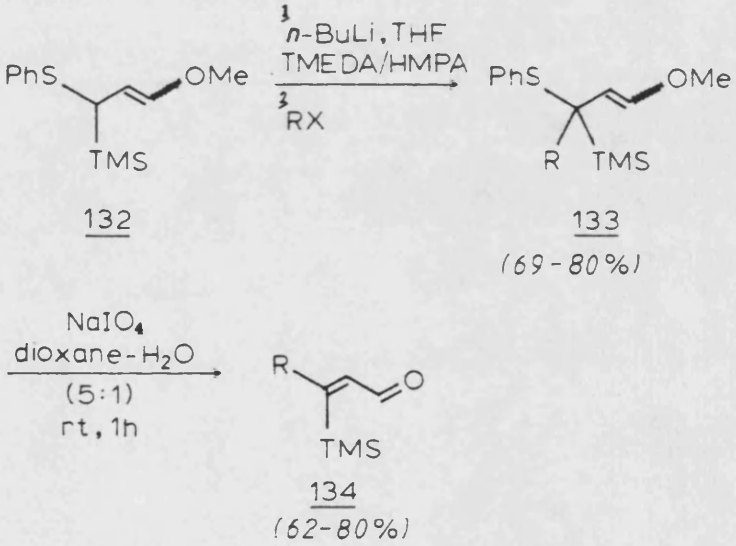
McDougal *et al.*[123] found that the vinyl sulphide 129, formed in the highly-stereoselective, base-catalysed elimination from the 3-(phenylthio) analogue of 117 and 121, could undergo site-selective deprotonation with *s*-BuLi in DME, so that only the vinyl proton was abstracted (Scheme 56).



Scheme 56

This very interesting result contrasts with mono-Y-oxyvinyl sulphides such as 123, which undergo allylic deprotonation.[122,124] The additional oxy substituent is thought to act to diminish the acidity of the allylic proton while maintaining a chelating environment for vinyl deprotonation.[125]

Mandai *et al.*,[126] by analogy with Taguchi *et al.*, were also especially interested in ambident allylic anions stabilised by both sulphur and oxygen, because of the possibility of complete regioselective control upon alkylation. Alkylation of 1-methoxy-3-phenylthio-3-trimethylsilyl-1-propene 132 resulted in exclusive α-adduct formation 133, which was converted into 134 on treatment with periodate *via* a [2,3]-sigmatropic rearrangement (Scheme 57).

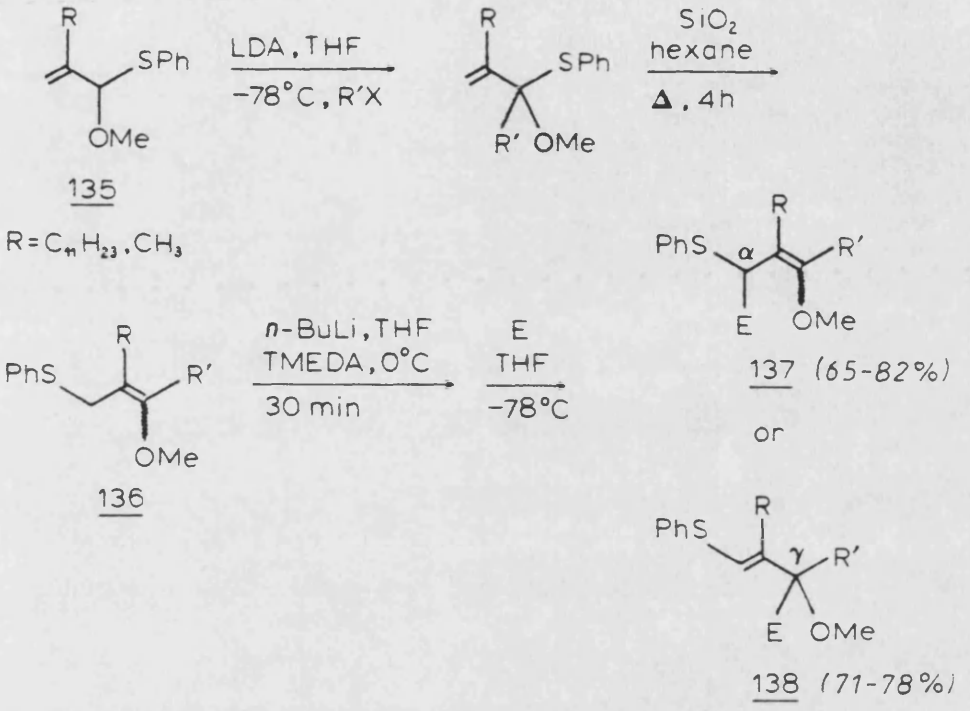


Scheme 57

Bearing in mind that 132 can also act as an acyl anion d^1 reagent, these findings build on Taguchi's work and allow 132 to be regarded as a novel homoenolate dianion equivalent.

Otera *et al.*[127] also discovered a compound exhibiting a binucleophilic character incorporating d^3 component reactivity. α-Methoxyallyl sulphides 135 were subjected to a sequence of an exclusive α-alkylation, an allylic rearrangement of the phenylthio

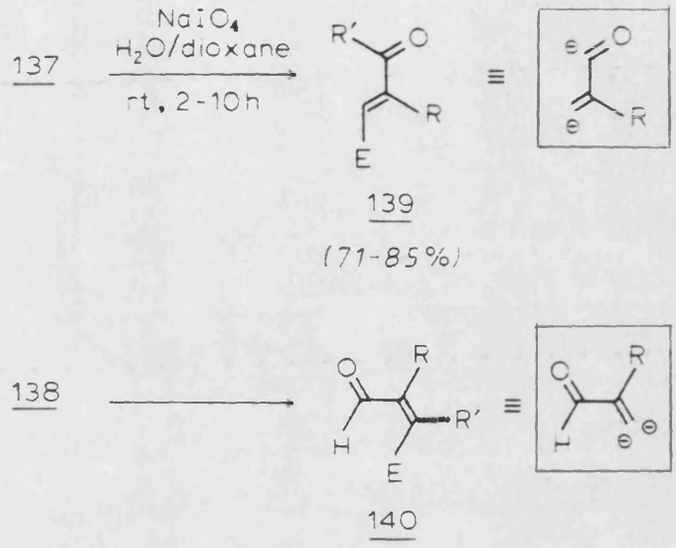
group to give 136, and regiospecific reaction of these γ-methoxy-allyl sulphides with electrophiles (Scheme 58). A simple and



Scheme 58. When E = RX, adduct **137** is obtained; when E = RCHO, adduct **138** is produced.

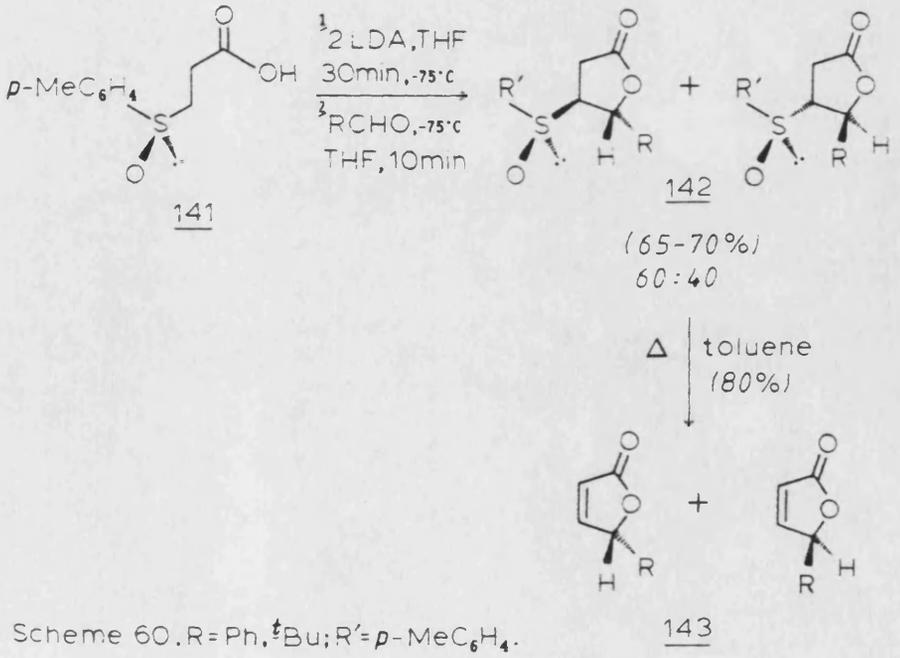
effective method was used to transform 137 to α,β- unsaturated carbonyl compounds 139, and with a similar transformation, 138 can be converted to 140, the product of β-dialkylation (Scheme 59).

The use of 3-phenylsulphinylpropionic acid 109 by Uda *et al.*[112] made no mention of applying a chiral sulphoxide in asymmetric induction at the α-sulphinyl position. However, as the sulphinyl group has been successfully used to obtain chiral d^1, d^2, and a^2 synthons[128] as well, Bravo *et al.*[129] used this group as a d^3 building block in the synthsis of optically pure 5- substituted furan-2(5H)-ones. (+)-(R)-3[(4-Methylphenyl)sulphinyl]propionic acid 141 was



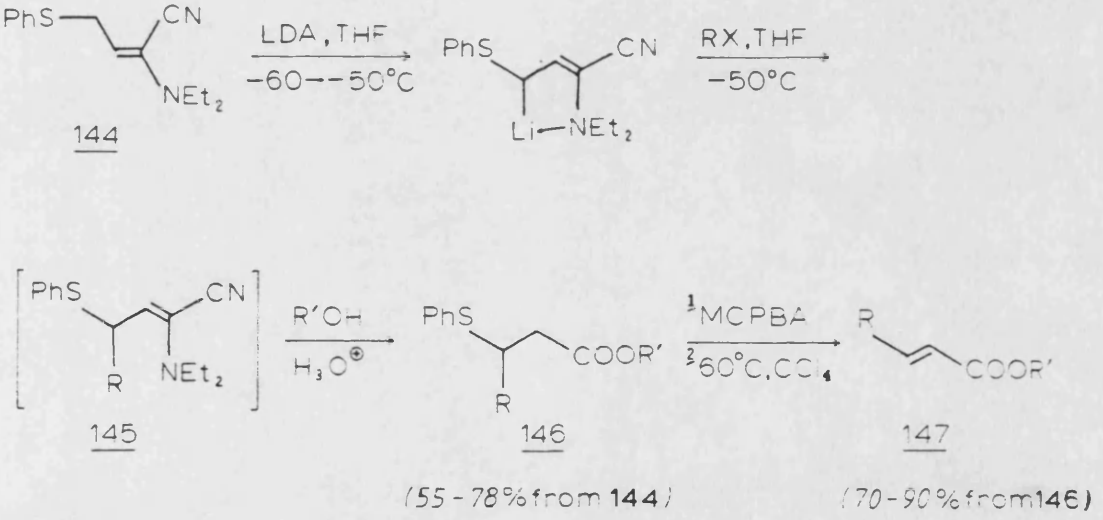
Scheme 59

dimetallated and reacted with an aldehyde to give the diastereoisomeric β-sulphinyl-γ-lactones 142. These could be separated and their pyrolysis afforded optically-pure 143 (Scheme 60).



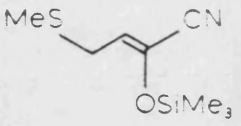
Scheme 60. R = Ph, ^{t}Bu; R' = p-MeC$_6$H$_4$.

Ghosez *et al.*[130] derived a reagent from α-cyanoenamines which could function as the equivalent of a β-carboxyl vinyl anion unit.[131] 2-Diethylamino-4-(phenylthio)-2-butenonitrile 144, prepared in 86% yield from the known 3-(phenylthio)propionic acid 108, was metallated with LDA and reacted with various electrophilic reagents, including acetaldehyde, and conjugated systems to which 144 added in a 1,4- fashion. 144 reacted exclusively at the γ- position, and compounds 145 were readily converted in good yields into the α,β- unsaturated acids or esters 147 by a known oxidation and thermolysis procedure (Scheme 61). This behaviour



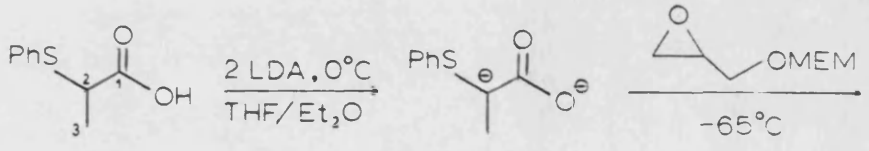
Scheme 61. R=primary alkyl(Br or I), allyl(Br), and secondary alkyl(I). Also used acetaldehyde, cyclopentenone, cyclohexenone. R'= H, Me.

contrasts with that of the anion of 2-trimethylsiloxy-4-(methylthio)-2-butenonitrile 148, which undergoes exclusively α-alkylation.[132]

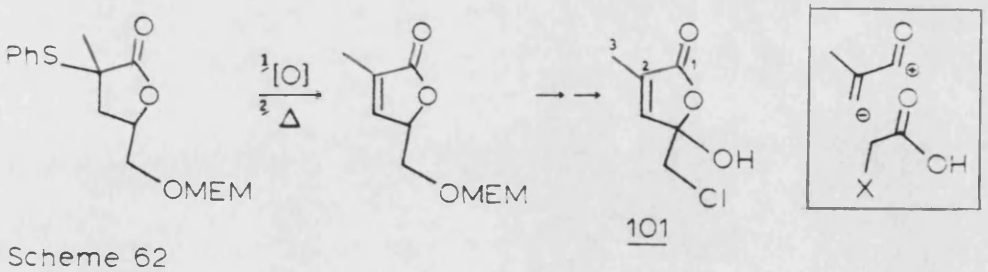


148

McMorris *et al.*[133] used the dianion of 2-(phenylthio)propionic acid[74,134] 149 as a building block in the synthesis of lepiochlorin,[105c] not as a d^3 reagent, but in what can formally be regarded as a d^3 synthetically equivalent reaction sequence (Scheme 62). The result is a formal incorporation of a 2-



149

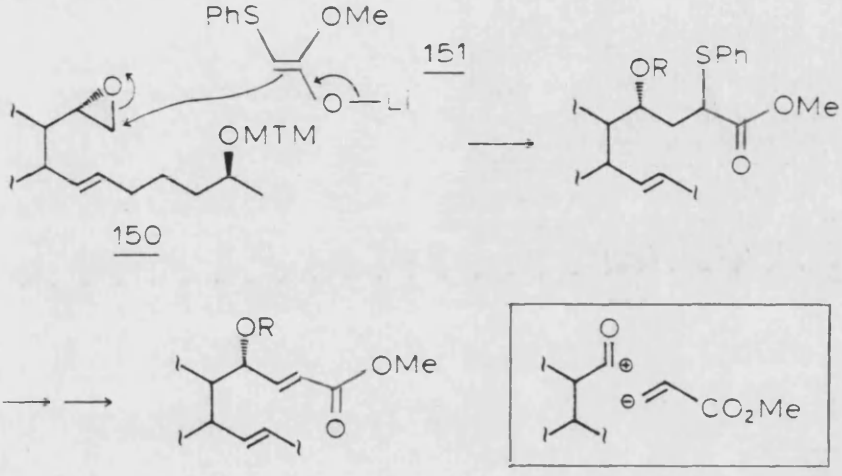


Scheme 62

methylacrylic acid unit into the butenolide, although the β sp^2 carbon atom originates from the epoxide.

Trost *et al.*[8k] used a synthetically equivalent d^3 reaction series to construct the enone system of brefeldin A; the β-

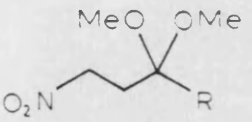
carbon atom being supplied by the epoxide 150, and remainder from methyl 2-lithio-2-(phenylthio)acetate[136] 151 (Scheme 63).



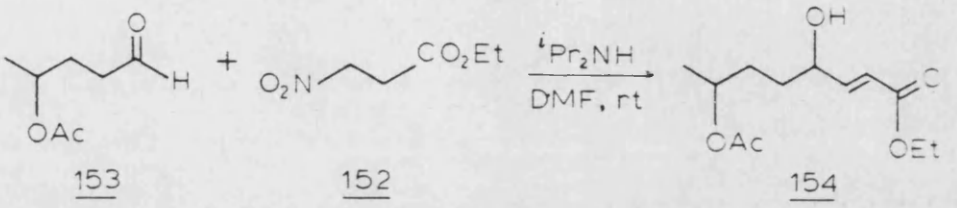
Scheme 63

The use of a 3-nitropropionate ester as a d^2 reagent has already been described in Section 1.2.2 (reference 68). However, 3-nitropropionate has also been used as an enone[137] or acrylic ester[138] d^3 reagent. Although nitro compounds are known to add readily to aldehydes and reactive enones under mildly basic conditions,[139] β-nitro esters, lactones, ketones and phosphonates eliminate nitrous acid under similar conditions to give unsaturation. The design of an acrylate d^3 reagent from such compounds therefore depends on bond formation preceding elimination.

Bakuzis *et al.*[138a] employed ethyl 3-nitropropionate 152 in a one-pot sequence not requiring anhydrous conditions in reaction with the γ-acetoxy aldehyde 153 to give the γ-hydroxyacrylate unit 154, which could be further elaborated to pyrenophorin (Scheme 64). With ketones, however, the elimination reaction was faster, necessitating the use of the protected compound 155.



155

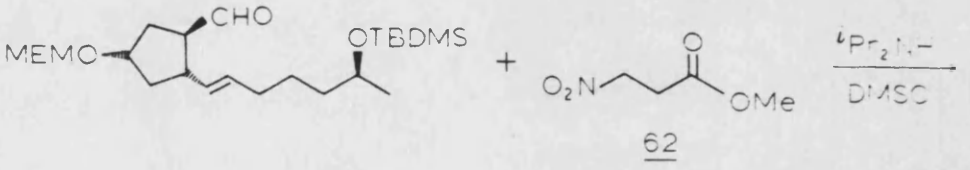


153 152 154 (38%)

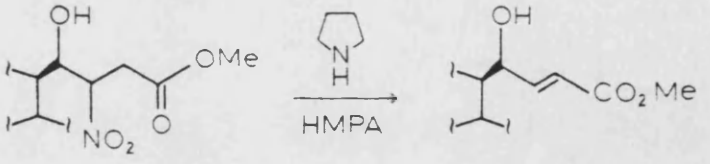
3

Scheme 64

Mori, Kitahara *et al.*[8f] constructed the γ-hydroxyacrylate portion in their total synthesis of (+)-brefeldin A using methyl 3-nitropropionate[138c] 62 as an acrylate d^3 synthon, employing mild basic conditions (Scheme 65).



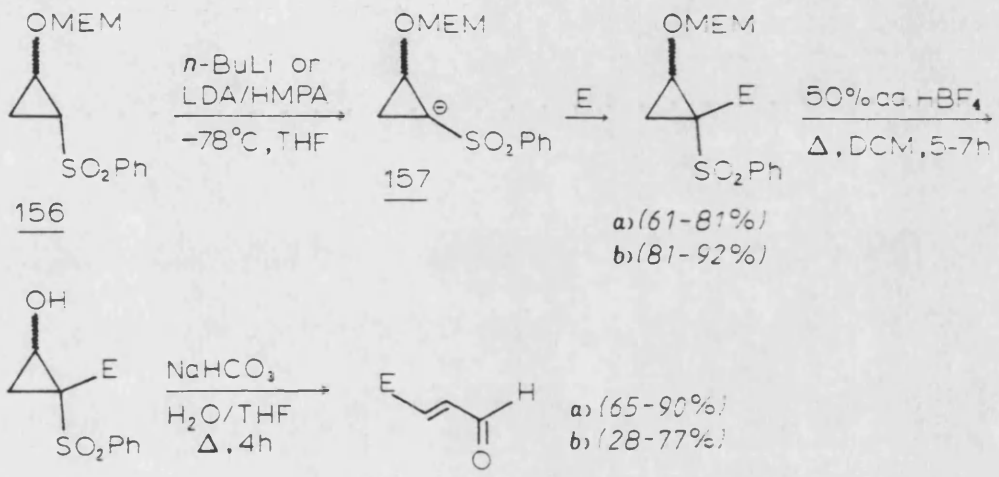
62



Scheme 65

One simple solution to the problem of homoenolisation in both a conceptual and operational sense, is the use of protected cyclopropanol derivatives. This approach has been used extensively for propionate d^3 reagents,[140] but for their use as acrylate d^3 synthons, an eliminatable group must be located on the carbon atom adjacent to that bearing the alkoxy function.

Pohmakotr *et al.*[141] used the anion of 1-[(2-methoxyethoxy)-methoxy]-2-phenylsulphonylcyclopropane 156 as a d^3 synthon; using the sulphonyl group as an α-carbanion stabilising moiety in the alkylation step, and as a leaving group to unmask the unsaturation (*cf.* 110, 114, 117 and 121) (Scheme 66).

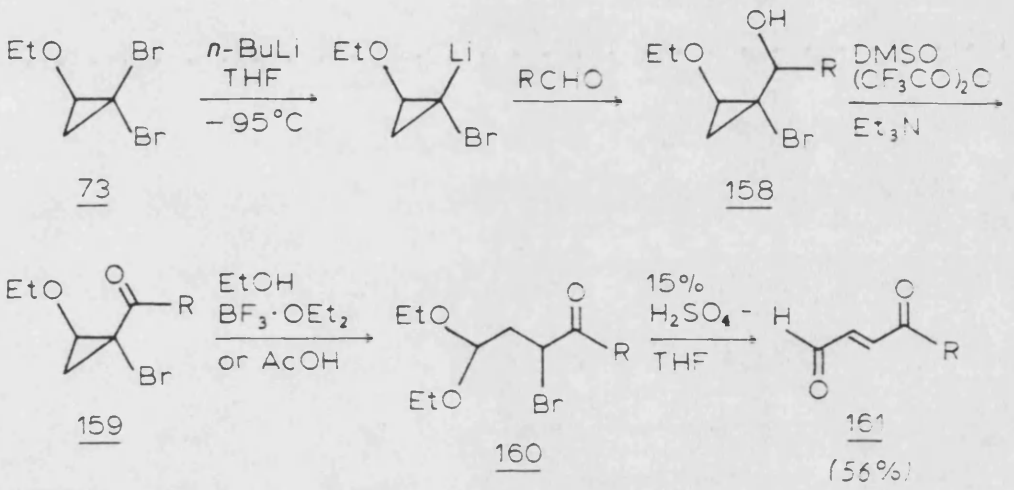


Scheme 66. *a*) Yields for primary *n*-alkyl bromides, allyl bromide; *b*) Yields for acetone, isobutyraldehyde, and benzaldehyde.

The anion 157 also reacts with aldehydes and ketones readily at -78 °C over 3 h. However, at higher temperatures, 0 °C or above, retro-aldol reactions take place, and only starting materials are recovered.

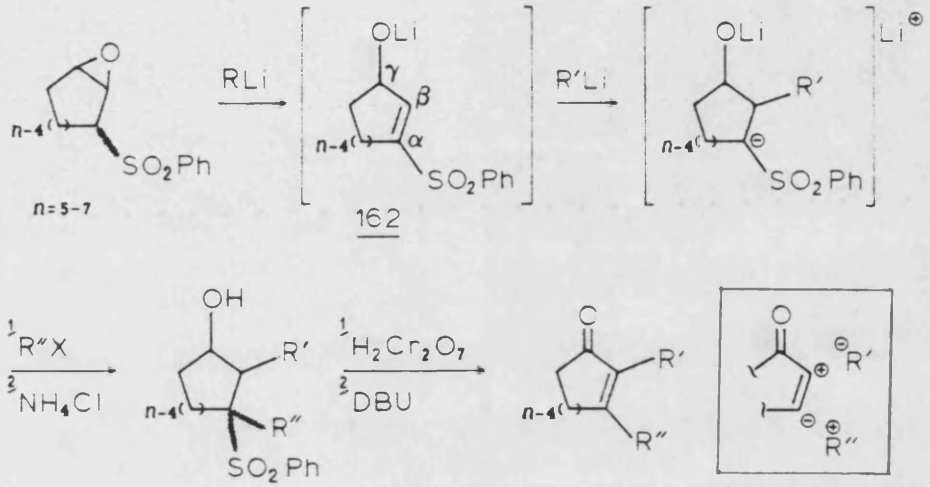
As already implied in Section 1.2.2, the potential ambident reactivity of the cyclopropanol derivative 73 used by Hiyama *et al.*[81] can be controlled by choosing a particular ring cleavage process. In this way, the tendency for 73 to act as a d^3 reagent can be highlighted. Hiyama *et al.* applied the known ring cleavage reaction of cyclopropyl ketone derivatives[142] to homologate a carbon skeleton. The initial hydroxyalkylation product 158 was

oxidised under Swern[143] conditions, to the acid-labile cyclopropyl ketone 159. Ring opening was followed by hydrolysis of the acetal 160, and dehydrobromination to give the γ-oxoacrolein 161 in 56% yield (Scheme 67).



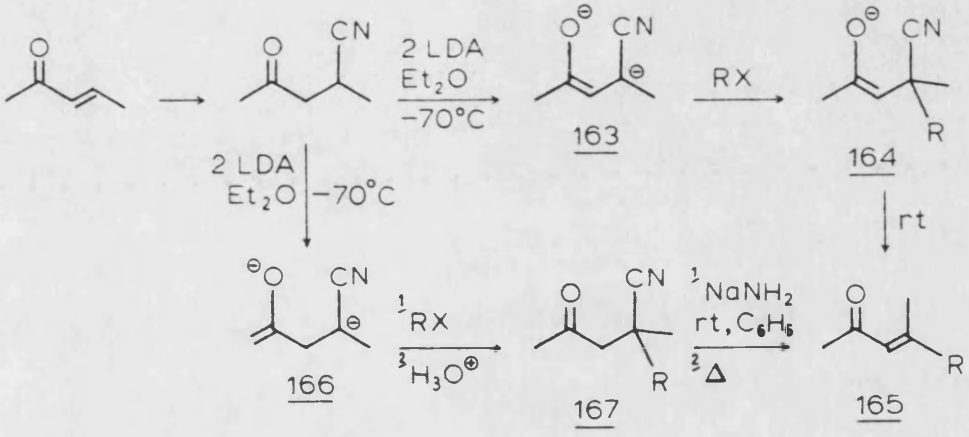
Scheme 67. R= n-C_6H_{13}.

Fuchs *et al.*[144] utilised another small ring system, that of an oxirane, to similar effect. As has been evident previously, a 3-sulphonyl group was used twice to direct deprotonation to the carbon atom to which it was attached. The 1,2-epoxy substituent was not strictly required for this reagent to express d^3 reactivity, but to establish a γ-oxido-α,β- unsaturated sulphone 162 to which a second carbanion could add conjugatively. In this way, both the α- and β- positions of an enone system could be functionalised, but in a manner in which the normal C-2 and C-3 reactivities were reversed (Scheme 68).



Scheme 68

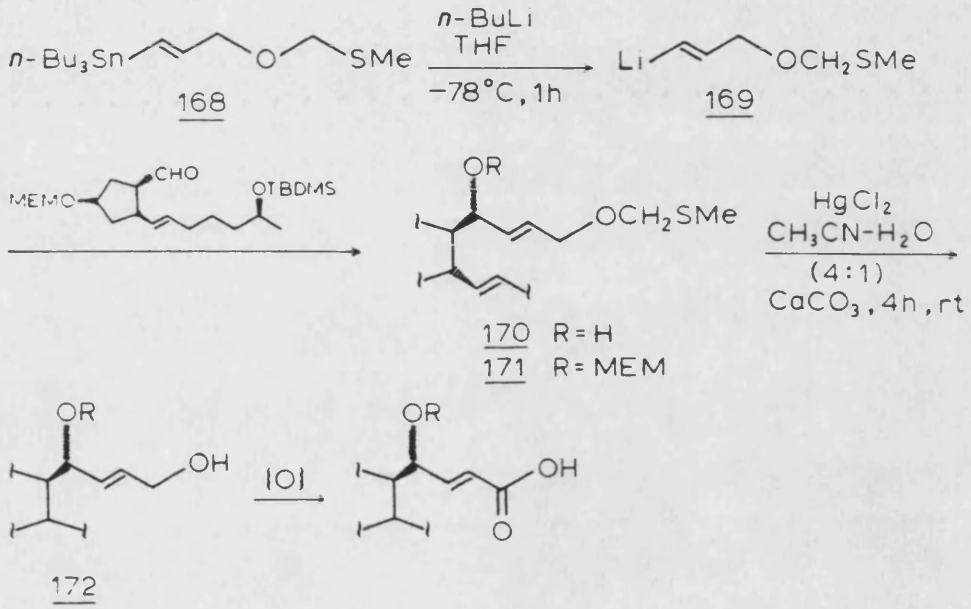
Larchevêque *et al.*[145] activated enone systems to exhibit d^3 reactivity by introducing the cyano group in a 1,4- addition.[146] In this procedure, it was not necessary to protect the carbonyl group during alkylation (*e.g.*, as a dioxolane) as had been the case with the sulphone acetals. The dianion 163 was prepared by removal of two protons from the keto-nitrile, and reacted with one equivalent of a primary alkyl halide resulting in alkylation of the less stable of the two anionic sites to give 164. The cyano group is eliminated spontaneously to give 165 in 70-79% yields by warming the reaction mixture to room temperature (Scheme 69). In cases where enolate 166 is formed, alkylation and hydrolysis give 167. Another enolate had to be formed under equilibrating conditions and at temperatures that favour cyanide elimination, and



Scheme 69

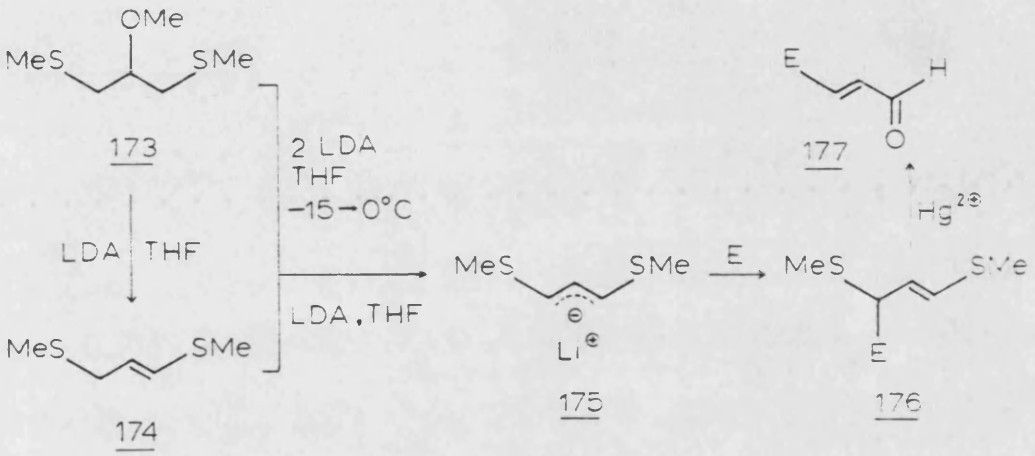
suppress the reaction of 164, or monoalkylated 166, with enone 165.

Another approach to the total synthesis of (±)-brefeldin A, this time by Corey *et al.*,[8c] revealed another acrylic d^3 equivalent employed to construct the γ-hydroxyacrylate unit. The tri-*n*-butyl vinyl stannane[147] 168 was transformed to the vinyl lithium compound 169 by tin-lithium exchange.[148] Efficient carbonyl addition formed the alcohol 170, which was protected. The methylthiomethylene group was removed using mercuric ion at ambient temperature to give the alcohol 172 which was oxidised to the corresponding acrylic acid (Scheme 70).



Scheme 70

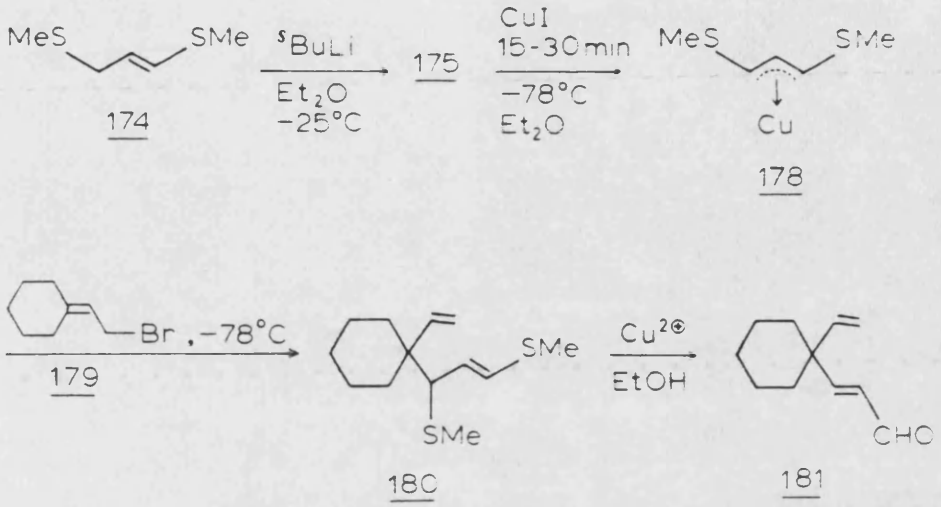
Corey *et al.*[149a,b] found that double metallation of 1,3-bis(methylthio)-2-methoxypropane 173, prepared in 76% yield from epichlorohydrin and sodium methanethiolate, resulted in a symmetrically-substituted allyl anion 175 that served effectively as a d^3 acrylic synthon in reaction with alkyl halides, carbonyl compounds, and 1,2-epoxides,[149c] (Scheme 71). The reagent has also been applied to the total synthesis of prostaglandin $PGF_{2\alpha}$.[149b]



Scheme 71. E = 1-bromopentane, propanal, cyclohexene oxide; yield of 177 = 84, 41, and 82% respectively.

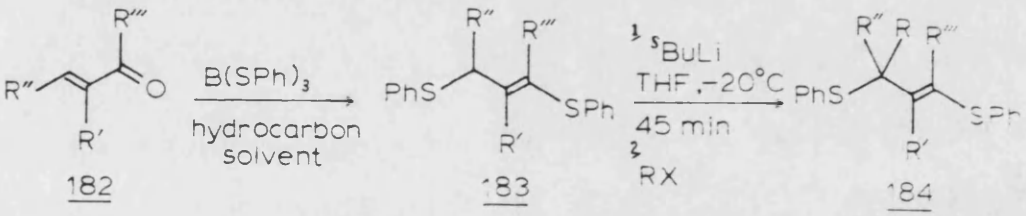
Yamamoto *et al.*[150] examined the corresponding 1,3-bis(methylthio)allyl copper(I) reagent 178, prepared from 175 in the absence of secondary amine. The reaction of 178 with allyl bromide 179 took place quantitatively by S_N2' mechanism to give 180. Hydrolysis of 180 was achieved under milder conditions than those used for 176, employing cupric instead of mercuric ion,[151] affording pure 181 in high yield (Scheme 72).

Cohen *et al.*[152] showed that the analogous 1,3-bis(phenylthio)-alkene derivatives 183 could be prepared directly from aldehydes and ketones 182, using triphenyl thioborate reagent, with few exceptions. The lithio derivatives were formed readily and alkylated efficiently to give 184 in 90-98% yields (Scheme 73).



Scheme 72

(92% from 179)



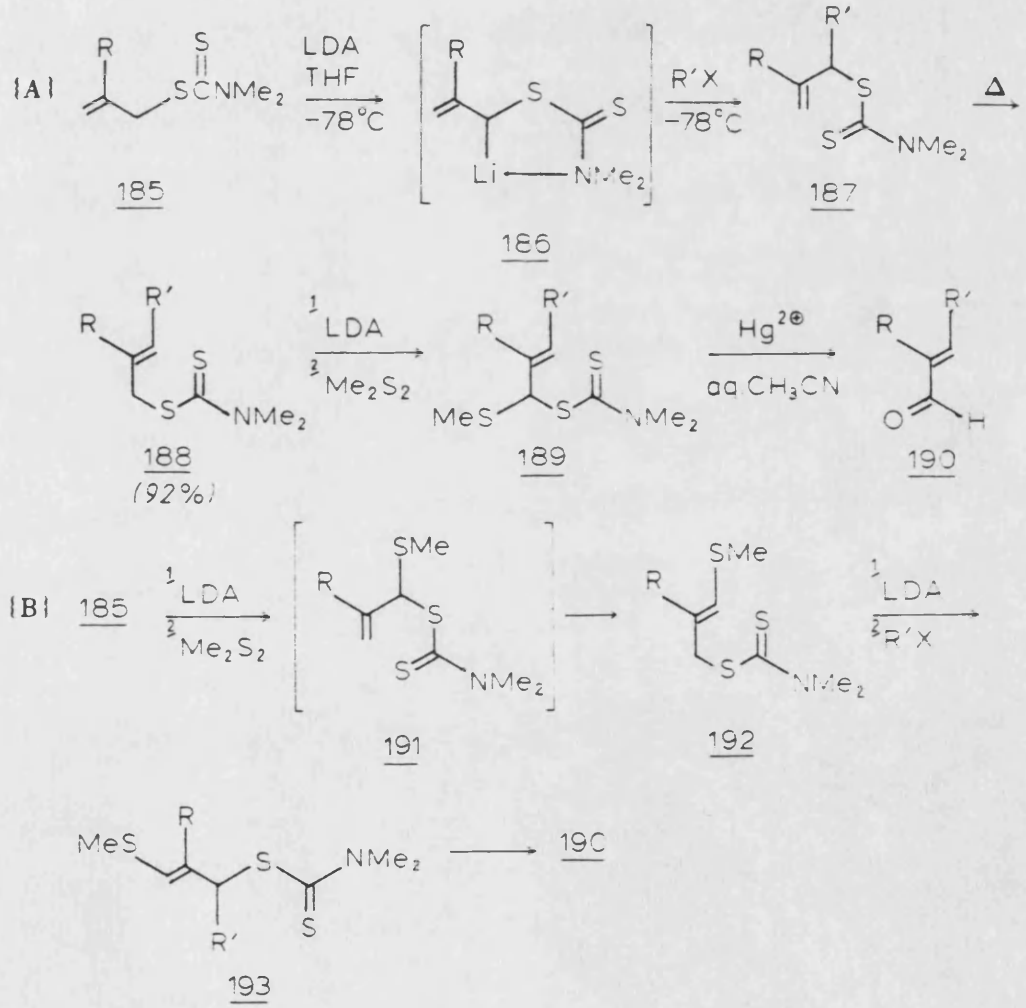
(90-98%)

Scheme 73

Cohen found that highly substituted derivatives 184 could be hydrolysed in a procedure using cuprous triflate that was superior to that using mercuric ion.[153]

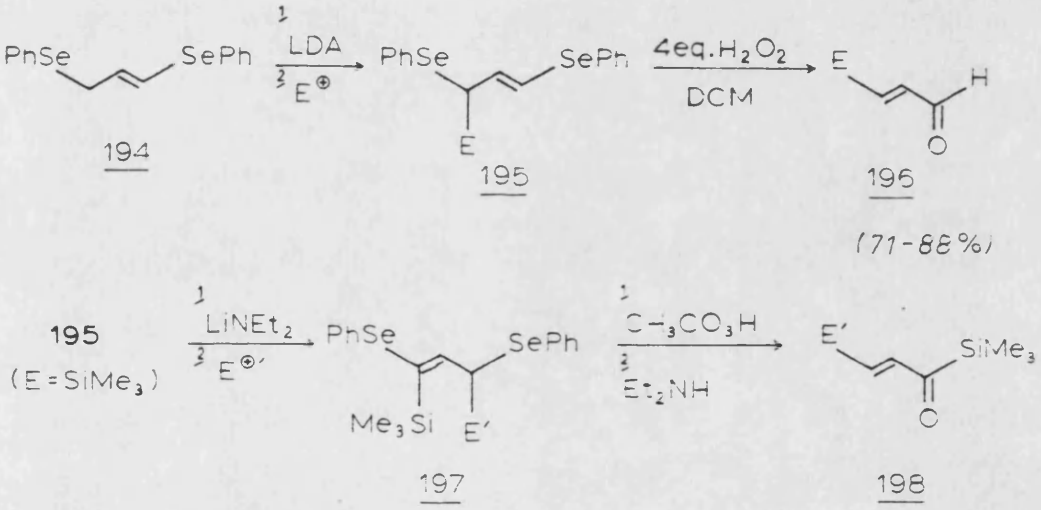
Nakai *et al.*[154a] employed S-α-lithioallyldithiocarbamates 186 as enone d^3 reagents.[154b] The *N*,*N*-dimethyldithiocarbamate moiety assisted in the regioselective alkylation of 185, the α-lithio

species perhaps being stabilised by chelation.[155] The tandem construction of the enone carbon-carbon double bond, and the masked carbonyl group involved a [3,3]-sigmatropic rearrangement of 187, followed by a sulphenylation reaction. (E)-α,β- unsaturated aldehydes were obtained exclusively on hydrolysis, this latter operation reported to be more rapid for 193 than for the somewhat analogous 176, and explained in terms of a stronger affinity of the dithiocarbamate moiety for mercuric ion[156] (Scheme 74).



Scheme 74. R′X = *n*-amyl iodide; **A)** alkylation, then sulphenylation; **B)** vice versa.

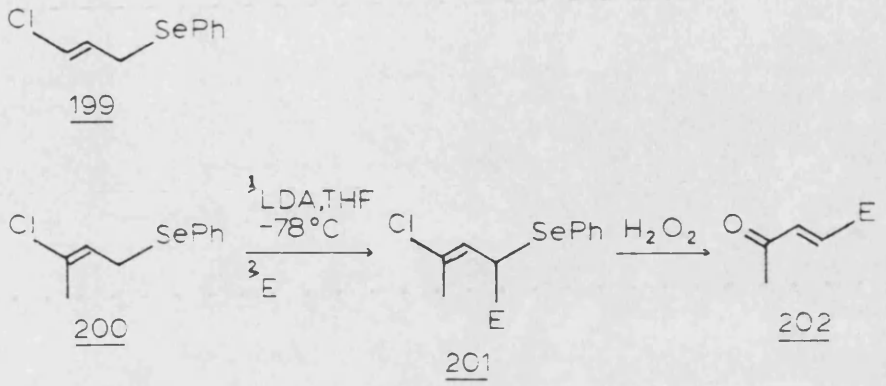
Reich *et al.*[157] reported that 1,3-bis(phenylseleno)propene[158] 194, prepared from 1,3-dichloropropene, could be rapidly deprotonated with LDA at -78 °C to afford a reagent which, in reaction with alkyl halides, epoxides, aldehydes, ketones and chlorotrimethylsilane, could be utilised as a propenone d^3 synthon.[158d] The products 195 were smoothly converted to (E)-3- substituted propenal derivatives in 71-88% yields under unusually mild oxidative conditions (Scheme 75). Attempts to deprotonate 1-chloro-3-(phenylseleno)-1-propene 199, an isolable precursor of 194, proved



Scheme 75

unsuccessful,[157] whereas 3-chloro-1-(phenylseleno)-2-butene 200 could be metallated and alkylated, and served as a propenone d^3 reagent[159] (Scheme 76).

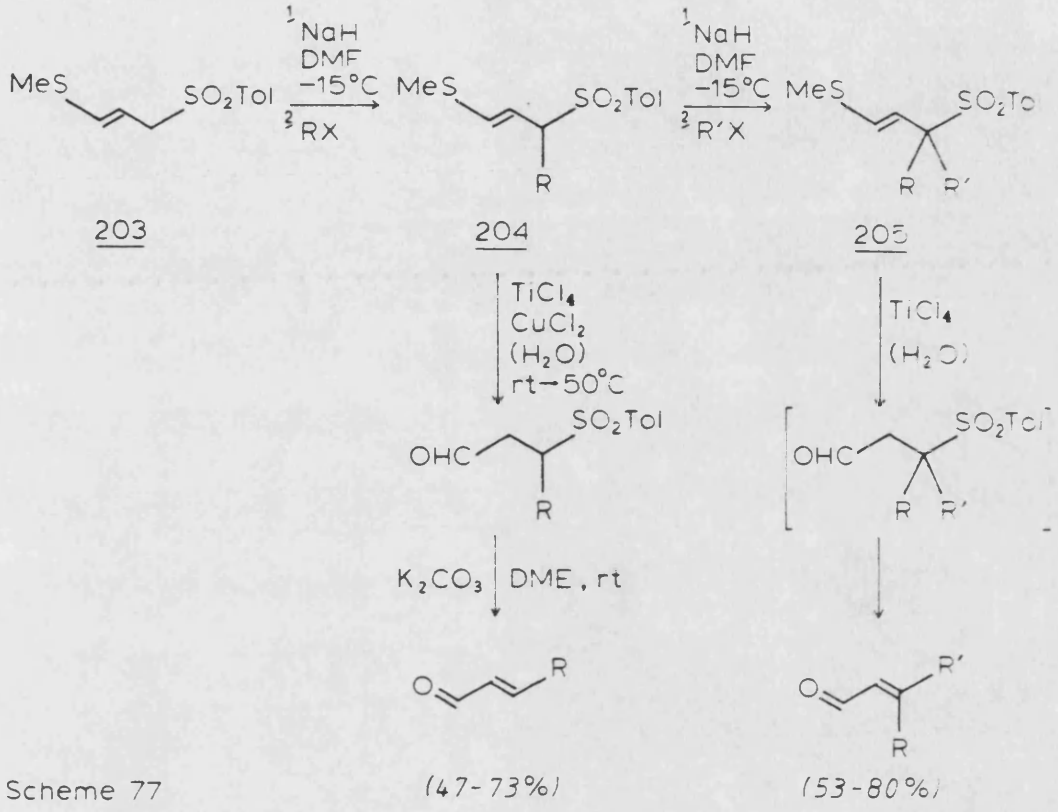
Ogura *et al.*[160] employed 3-methylthio-2-propenyl *p*-tolyl sulphone 203 to prepare β-mono- and β,β- disubstituted acrolein derivatives. 203 could be optionally mono- or di-alkylated to give 204 and 205 respectively using an easily handled base; the second



Scheme 76. When E = 1-bromo-2-phenylethane, 1,2-epoxypropane, benzyl bromide, and dimethyl phenyl silyl chloride, yield of 202 = 85, 80(acetylated product), 70, and 63% respectively.

alkylation taking place at the same carbon centre as the first (*cf.* compound 174). Subsequent acid hydrolysis of the vinyl sulphide portion using titanium tetrachloride,[161] was followed by elimination of *p*-toluenesulphinic acid to afford the functionally substituted α,β- unsaturated aldehydes (Scheme 77).

The monoalkylation of unsymmetrical heteroatom substituted allylic anions has been extensively studied.[162] The ambident character of these carbanions, with two potentially attacking atoms, often results in mixtures, although electrophiles are intercepted with a high degree of α-regioselectivity.[163] In certain cases, these anions (which normally serve as carbonyl d^1 and propionate d^3 equivalents) can be used to construct acrylic d^3 reagents. Mild oxidation of the 3- substituted allyl alcohols 208, obtained *via* [2,3]-sigmatropic rearrangement of the sulphoxide,[164] or selenoxide[165] 207, should afford the required β- substituted enones 209.

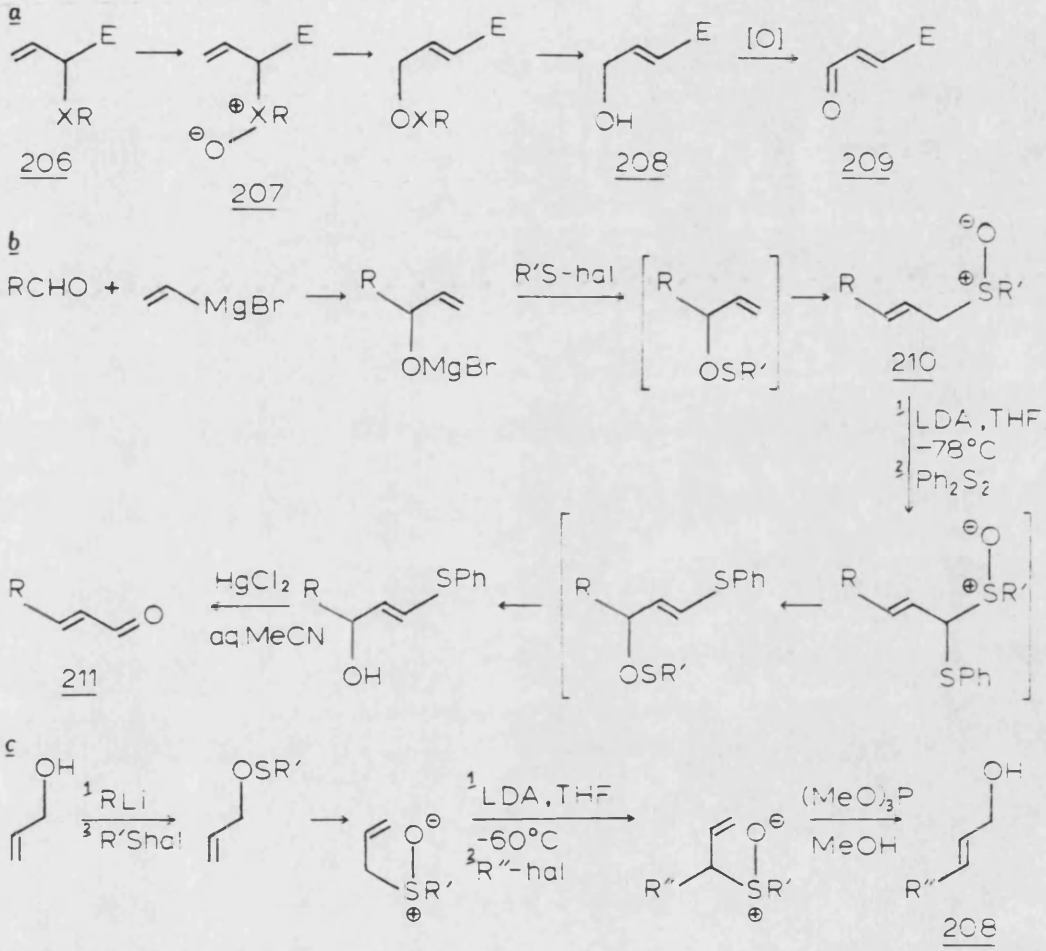


203 204 205

Scheme 77

When the allyl sulphide or selenide 210 already contains a substituent (R), an alkylation, with a disulphide for example, provides a synthetically equivalent d^3 reaction sequence whereby R can be located at the 3- position of acrolein 211.[166] The methodology can be directly applied to allyl alcohols (Scheme 78).

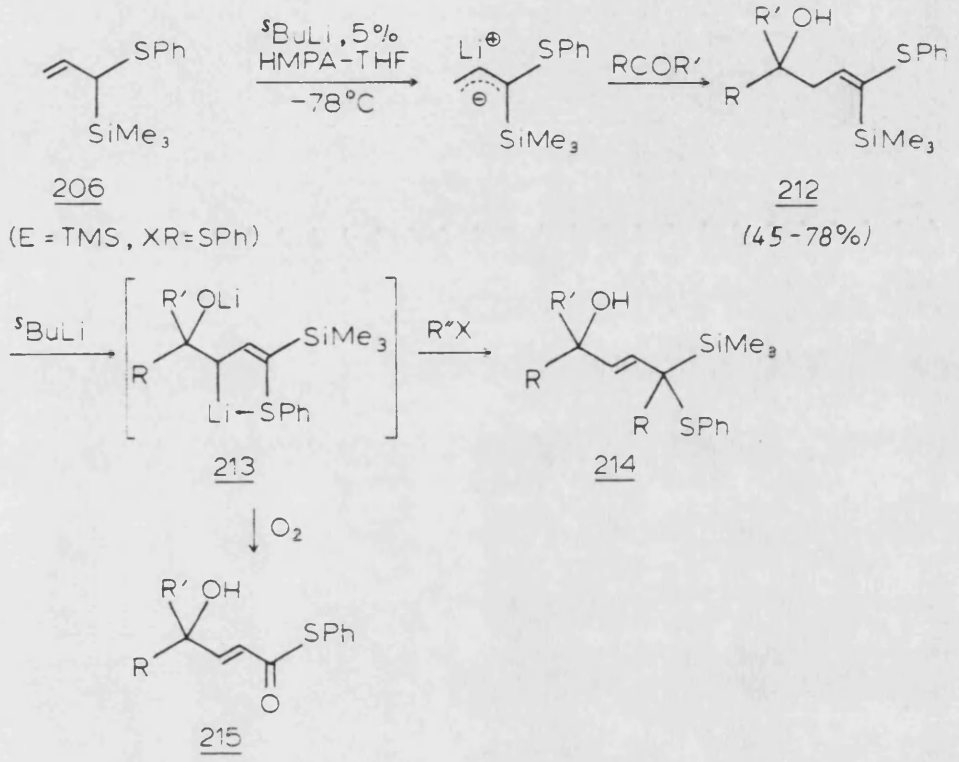
By incorporating an α-trimethylsilyl group (206, E = TMS, XR = SPh), Watt *et al.*[167] were able to direct alkylation to the γ- position, the masked propenone d^3 reagent being revealed in a second alkylation step (Scheme 79). The anticipated dimetallation of 212 leads to a dianion 213 in which the steric and/or



Scheme 78. X = S, Se.

electrostatic interaction involved in reaction with a second electrophile at the γ- site directs attack exclusively to the α- site with a variety of primary and secondary alkyl halides. Oxidative desilylation of 213 affords γ-hydroxy-α,β- unsaturated thiol ester derivatives 215.

γ-Alkylation of various ketene dithioacetals, which can also be included in the present category, also results in β- functionally

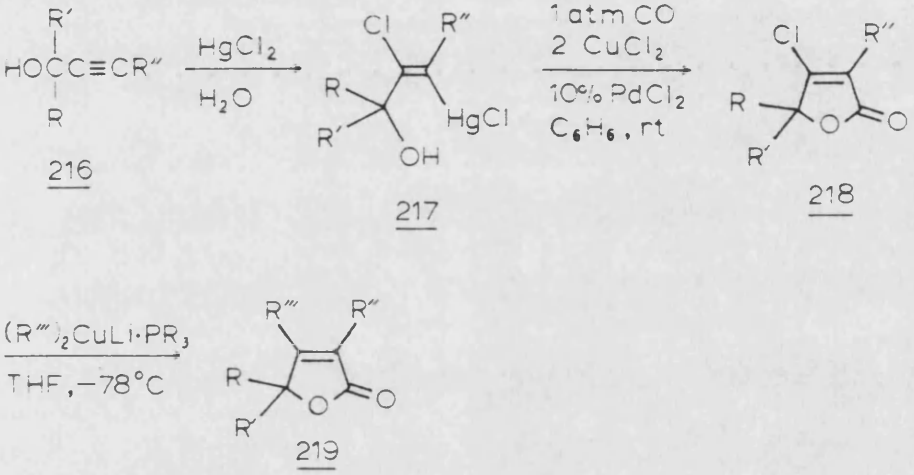


Scheme 79. R, R' = H, alkyl; R" = primary, secondary alkyl.

substituted acrylic compounds if provision is made to re-introduce the carbon-carbon double bond. The use of ketene dithioacetals in this way will be more fully described in the discussion.

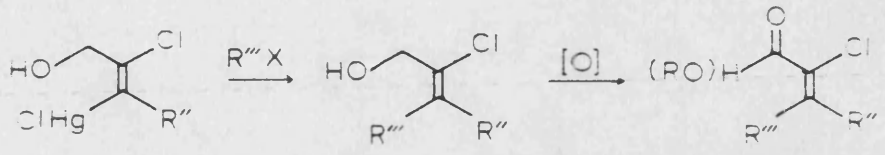
Larock *et al.*[168] found that mercuric chloride readily adds to relatively low molecular weight propargylic alcohols 216 containing either a primary or tertiary hydroxyl group (secondary propargylic alcohols do not precipitate vinyl mercurial products). The resulting (E)-β-chloro-γ-hydroxyvinyl mercuric chlorides 217 can be

carbonylated in near quantitative yield by stirring with *ca.* 10% $PdCl_2$ and two equivalents of $CuCl_2$ in benzene under carbon monoxide to give the β-chlorobutenolides 218 (Scheme 80).



Scheme 80 . R and R′ = both H or both alkyl; R″ = H , alkyl; R‴ = alkyl .

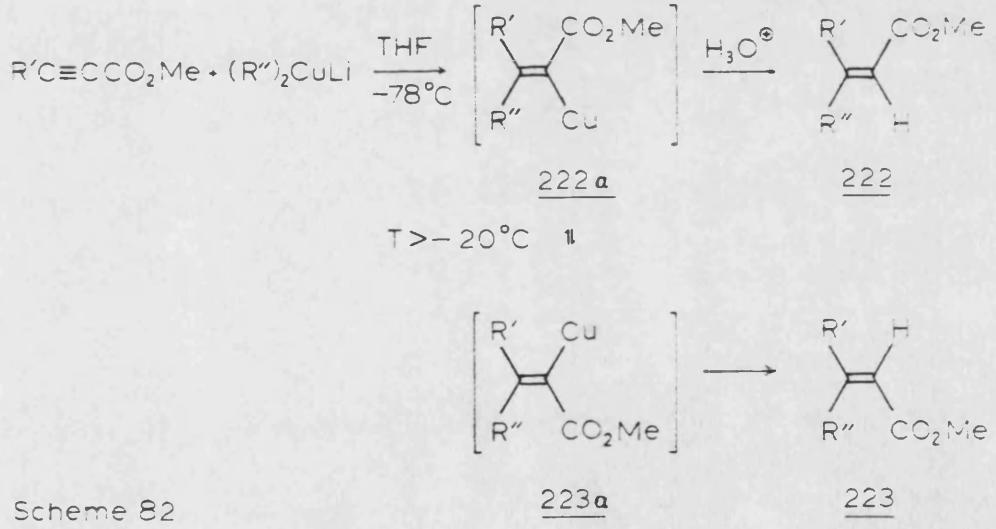
The carbonylation reaction, apart from the required introduction of the carbonyl group itself, was also used to establish an enone system capable of conjugatively receiving certain Gilman reagents which appear to react instantaneously to give β-alkylbutenolides 219 (itself a d^3 synthetically equivalent reaction sequence). However, one can envisage the HgCl group being replaced in the primary alcohol derivative 217 by other electrophilic reagents and the primary alcohol mildly oxidised (Scheme 81).



217 220 221

Scheme 81. Protection of 221, or direct use of 220 prior to oxidation, could also give rise to an acrylic d^2 equivalent.

Although Corey *et al.*[169] used the conjugate addition of lithium dialkylcuprates to α,β-acetylenic esters to form tri- and tetra-substituted alkenes,[170] the overall result is that of using an acrylate d^3 reagent (Scheme 82).



222a 222

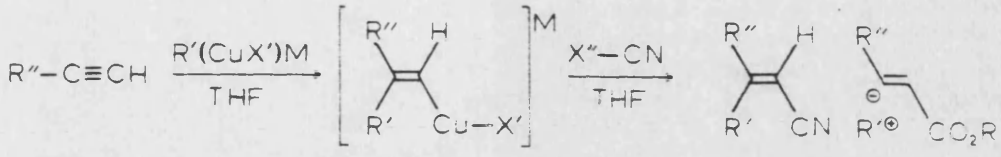
T > −20°C ⇅

223a 223

Scheme 82

At low reaction temperatures, the cuprate adds exclusively *cis*, and 222 was obtained in very high yield, but as the temperature was raised, more of 223 was produced due to equilibration of the intermediate copper enolates 222a and 223a.

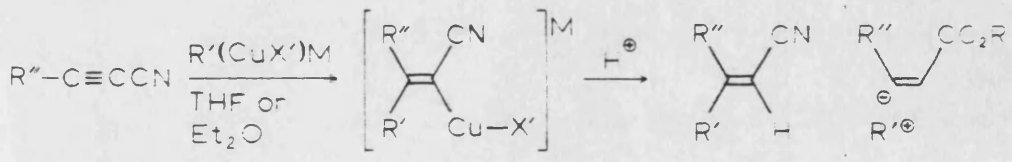
Vermeer *et al.*[171a,b] obtained vinylcuprates 225 stereospecifically by adding alkyl cuprates to 1-alkynes 224. 2-Alkenenitriles 226 were efficiently and stereospecifically synthesised from 224 and suitable cyanogen sources (Scheme 83).



224 225 226

Scheme 83. R′=alkyl; R″=H, alkyl, Ph; M=MgCl, MgBr; X′=Br, alkyl; X″=Cl, $PhSO_2$, *p*-$MePhSO_2$.

In the above scheme, the relationship between the cyano group and R^1 can be made (E) if the cuprate is added to 2-alkynenitriles[171c] 227. Hydrolysis of the cuprate 228, affords the nitriles 229 in 75-98% yields (Scheme 84).

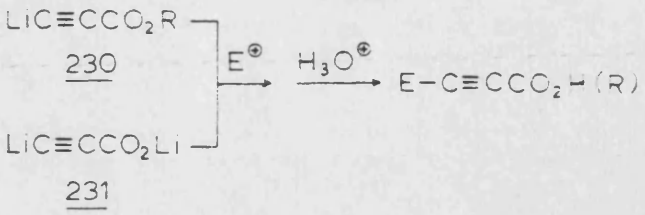


227 228 229

(75-98%)

Scheme 84. R′, R″= alkyl, vinyl, Ph; X′=Cl, Br, I, R′; M=Li, MgCl, MgBr.

The carbonyl function of acetylenic carboxylates is also well enough protected if it is simply present as the carboxylate anion. Thus, both the β-lithio propiolate ester 230, and the corresponding lithium carboxylate 231 will β-alkylate to afford the 'same' product after hydrolysis (Scheme 85).

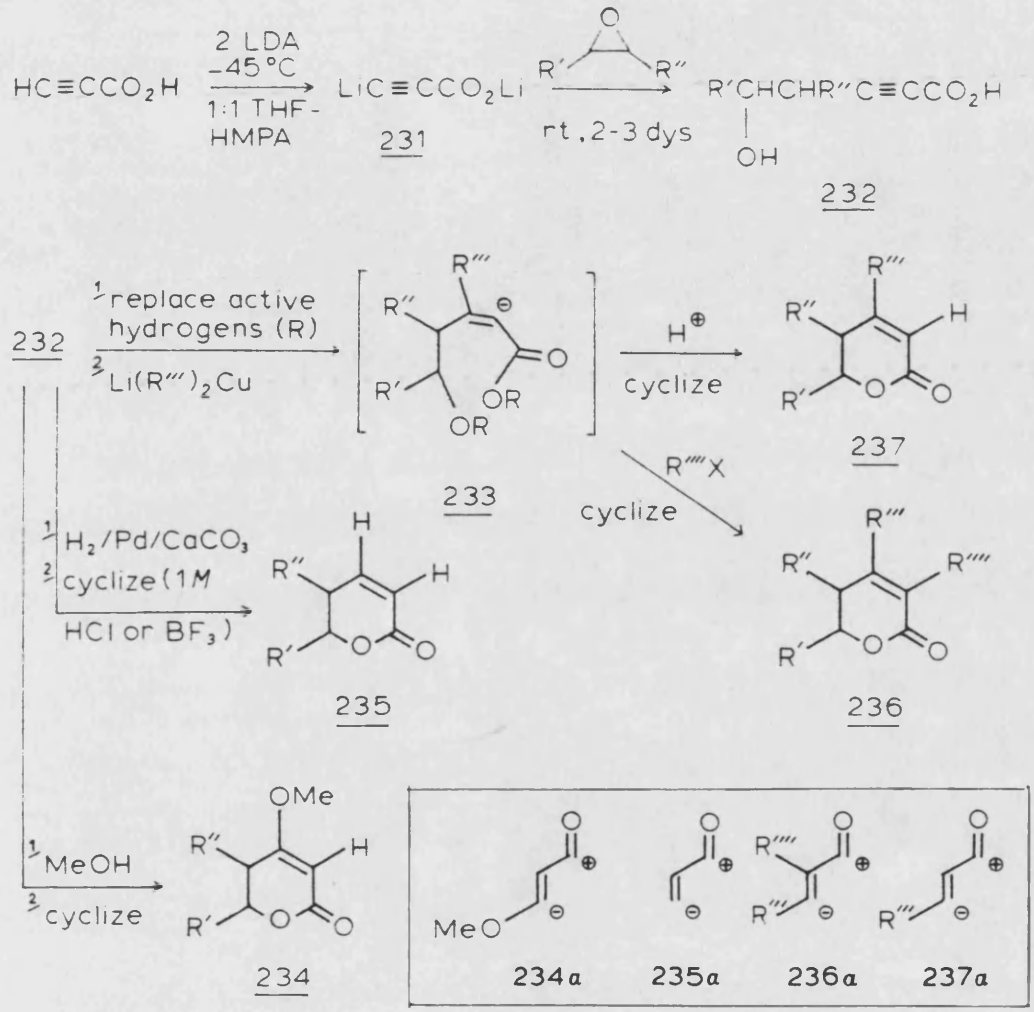


Scheme 85

In addition, the use of HMPA cosolvent overcame the normally observed sluggish reactivity of alkali metal acetylides towards many electrophiles,[172] which had previously resulted in only a few additions to aldehydes, ketones, and epoxides being described.[173,174]

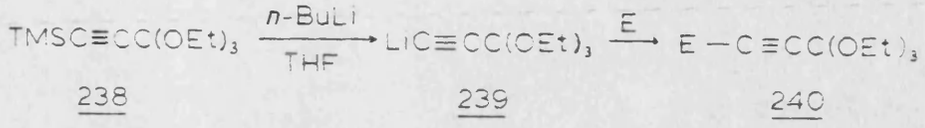
Carlson *et al.*[10c] chose the dianion 231 as a stable 3-carbon nucleophile[175] in the presence of HMPA in reaction with epoxides, due to the pronounced difference in the thermal stability of 230 *versus* 231.[176] The resulting δ-hydroxy-2-alkynoic acids 232 were transformed into 5,6-dihydro-2(2H)-pyranones with a variety of substitution patterns (Scheme 86).

The tendency of anion 230 to react at the carbonyl position of another β-lithio acetylenic carboxylate led Boche *et al.*[177] to using lithium ethyl orthopropiolate 239 in an acetylenic d^3 version of Stetter's ortho ester d^2 equivalent (Section 1.2.2, page 15). 239 was prepared from the corresponding β-silyl ethyl orthopropiolate 238, as there was no facile access in the literature to ethyl orthopropiolate itself[25] (Scheme 87).



Scheme 86. The formation of **233** and **235** employ both strategies used to form C=C of a d^3 acrylate synthon starting from a C≡C .

With more reactive electrophilic reagents such as aldehydes, use of 230 does not pose a problem, and Schmidt *et al.*[178] found that methyl propiolate functions as a simple and convenient precursor of acrylic d^3 reagent. Lithiation with LDA and reaction with aldehyde 242 gave, cleanly, adduct 243 in 92% yield. Hydrogenation of this compound in the presence of Lindlar catalyst



238 239 240

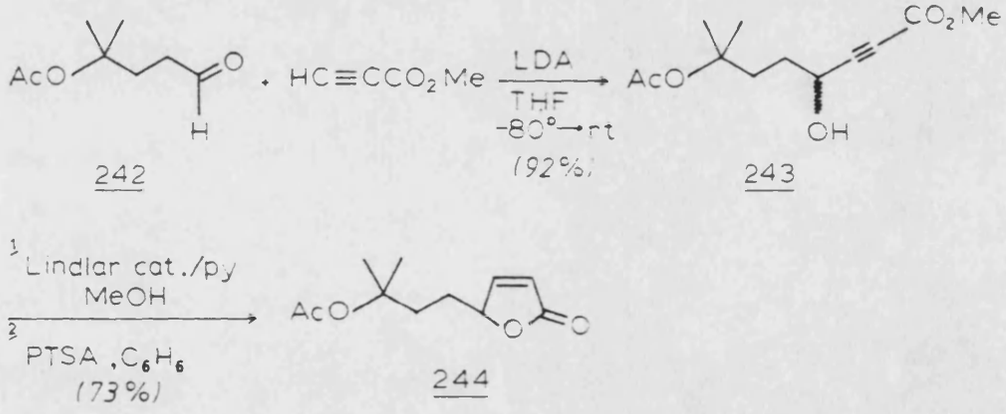
$HC\equiv C-C(OEt)_3$

241

E	Yield 240 (%)
RCHO, RCOR'	71-94
MeI	89 but requires TMEDA
BuBr	82 " " HMPA
Br	83 " " $CuBr\cdot Me_2S$
O	52

Scheme 87

and subsequent treatment of the reaction mixture with acid afforded butenolide 244 in 73% yield (Scheme 88).

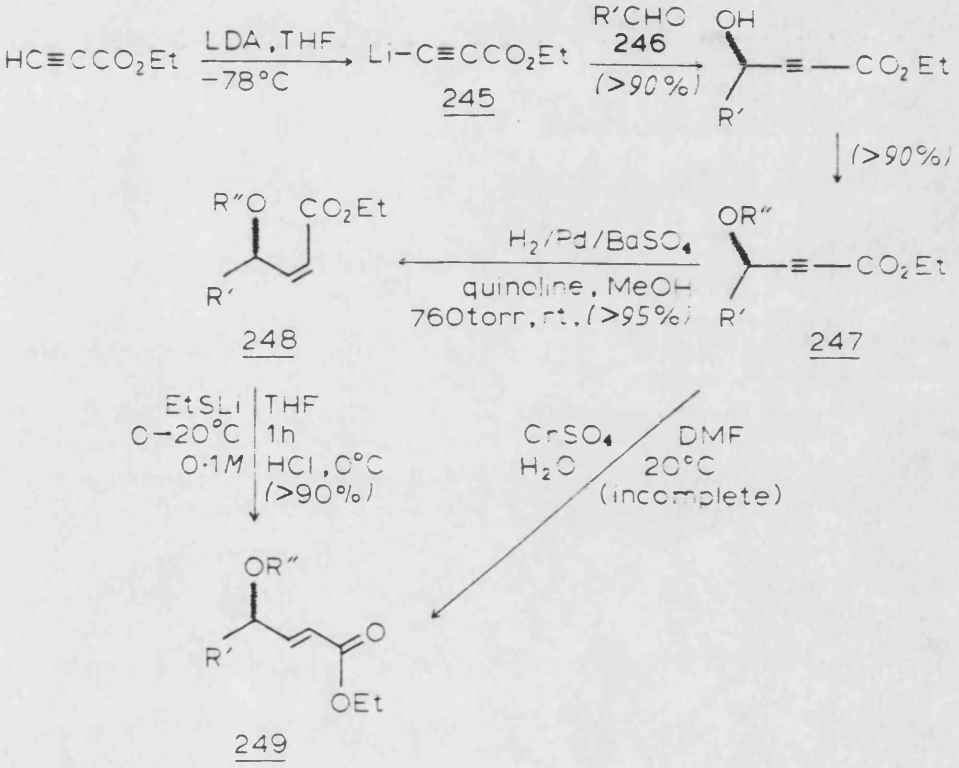


242 243 244

Scheme 88

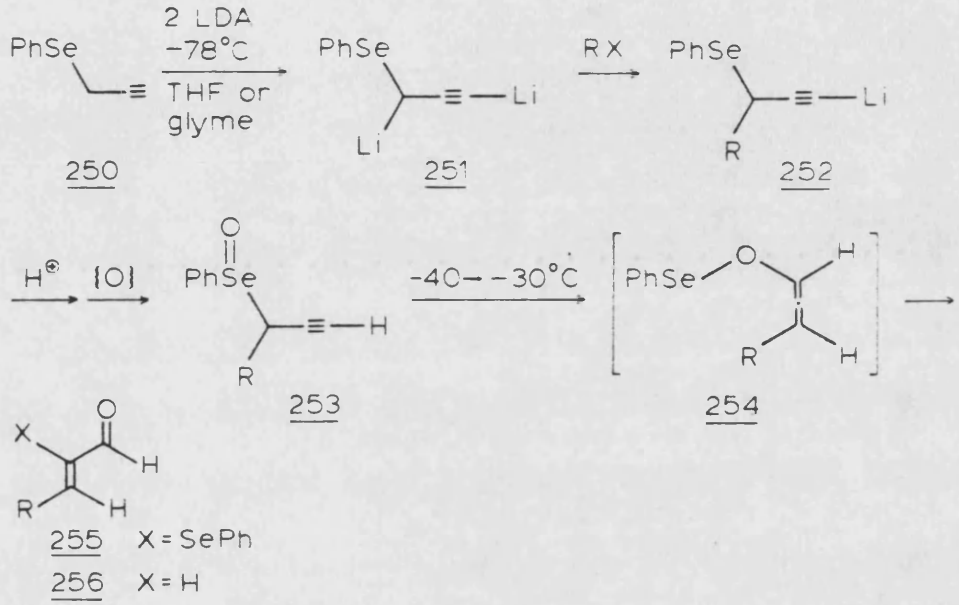
Gais *et al.*[179] had used a similar approach in the synthesis of the (E)-4-hydroxy-2-alkenoic acid function present in macrolides like brefeldin A. The lithium acetylide 245 derived from ethyl propiolate was reacted with aldehydes 246 in high yield, and the resulting alcohol was protected to give 247. Stereoselective reduction of the alkynoic ester was achieved by two stages. (Z)-

stereoselective reduction under Lindlar conditions was followed by (E)-stereoselective isomerisation. This route was more efficient than,and superior to,direct (E)-stereoselective reduction,[180] which did not go to completion in this case (Scheme 89).



Scheme 89

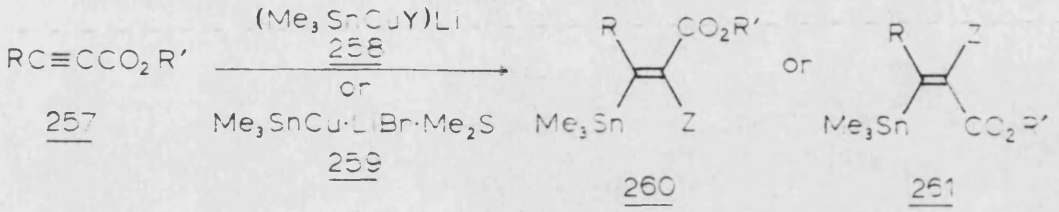
Reich *et al.*[181] used phenyl propargyl selenide 250 as an acrylate d^3 synthon[182] in a sequence whose key step was the rearrangement of the selenoxide 253 to the α-phenylselenoenone 255 at -40 to -30 °C, presumably *via* 254. Use of excess hydrogen peroxide in methanol achieved the conversion to 256 in moderate yields (Scheme 90).



Scheme 90. RX = 1° alkyl Br/I at −78°C; 2° alkyl I at −40°C.

β-Trialkylstannylacrylates can also serve as d^3 reagents by transmetallation,[183] or electrophilic destannylation,[184] but the preparation of these compounds *via* addition of trialkyltin hydrides to alkyl propiolates gives mixtures of regioisomers which are difficult to resolve.[185] The stereochemical problem has been solved with the use of trialkylstannylcopper reagents in reaction with acetylenic esters and β-halo acrylates.

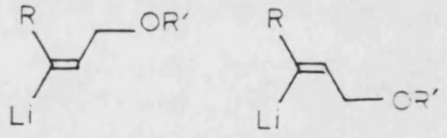
Piers *et al.*[186] showed that the propiolates 257 react smoothly with the copper reagents 258 and 259 to produce, after protonation of the intermediates, the conjugate addition products 260 or 261, the stereochemical course of reaction being controlled by choice of copper reagent and substrate structure (Scheme 91).



258 *a* Y = PhS[186b,g]
b Y = C≡CC(OMe)Me$_2$
c Y = Me$_3$Sn

Scheme 91. Z = H, Electrophile.

Reduction of the ester group, protection of the resulting alcohol and transmetallation (MeLi) of the trimethylstannyl group affords the synthons 262[102b] and 263[187] respectively, the corresponding d^3 equivalents of the (1-hydroxymethyl)vinyl anion of Schemes 37-39 (Scheme 92).

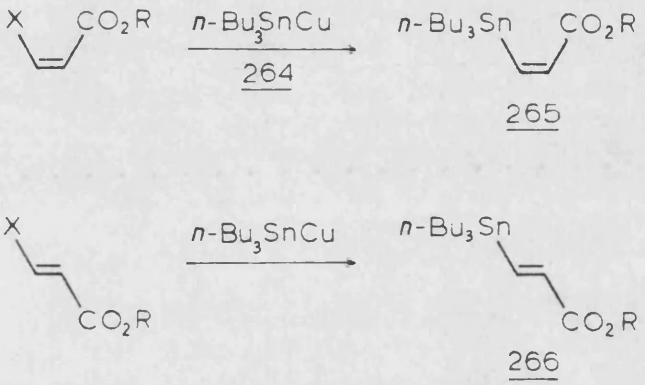


262 263

Scheme 92

Seitz *et al.*[188a] concerned themselves with approaches to the γ-oxygenated-α,β-unsaturated lactone moiety common to a number of macrocycles, and stated that 265 and 266 could act as intermediates in its synthesis.[189] The optimum conditions for the stereospecific syntheses of 265 and 266 from (Z)-[190] and (E)-3-haloacrylates respectively were reported. The best choice of R_3SnM reagent for

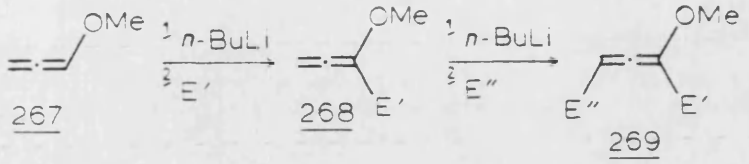
the required conjugate addition was chosen as the neutral tri-*n*-butylstannylcopper adduct 264, and the corresponding organostannanes could then be used for further carbon-carbon bond formation[188c] (Scheme 93).



Scheme 93. X = Cl, I.

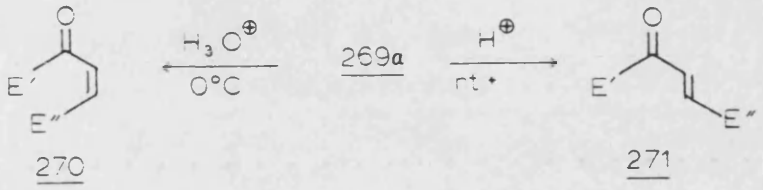
A number of allenyl lithium reagents have been developed for umpolung of the normal a^3 reactivity of the propenone unit.[191a] Clinet and Linstrumelle[192a] showed that methoxyallene 267 could be successively metallated with *n*-butyl lithium, and alkylated to afford an allene derivative 269 which yielded either (Z)- or (E)-substituted enones, 270 or 271 depending on the nature of the electrophile and the experimental conditions of the acid hydrolysis. By incorporating a temporary masking group E', metallation could be directed solely to the C-3 position providing an optional synthesis of 3- substituted acrolein derivatives[192b] 272 (Scheme 94).

In this way[7b] the 4-oxo-2-alkenoate unit present in some biologically-active natural products was prepared in a new synthesis of pyrenophorin 3 (Scheme 95).

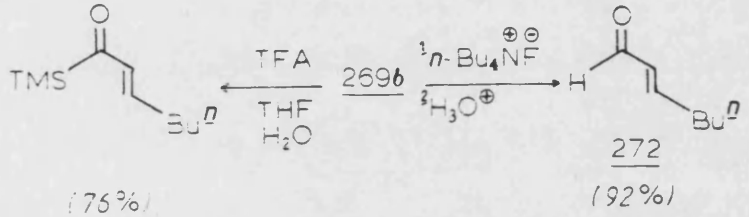


267 268 269

a) E' = n-C_5H_{11} ; E'' = SMe, TMS
b) E' = TMS ; E'' = n-Bu



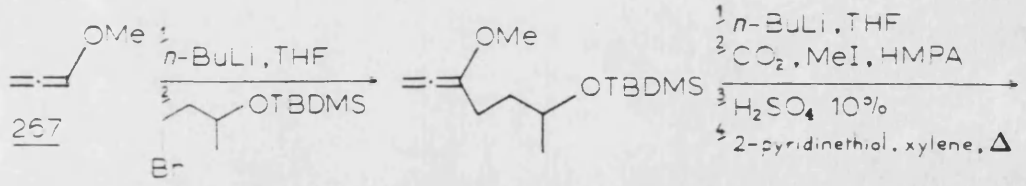
270 271



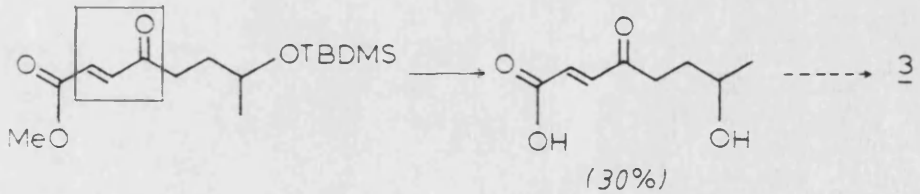
272

(76%) (92%)

Scheme 94



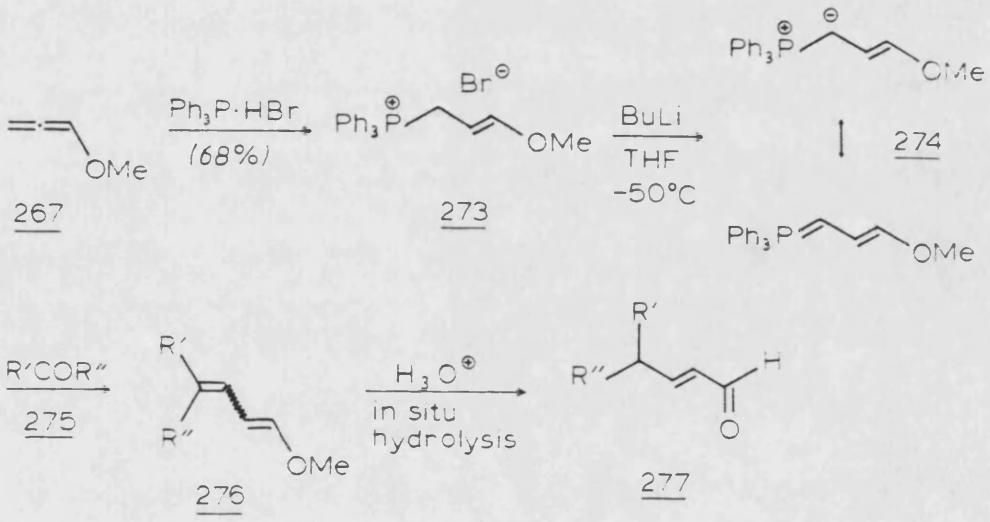
267



(30%)

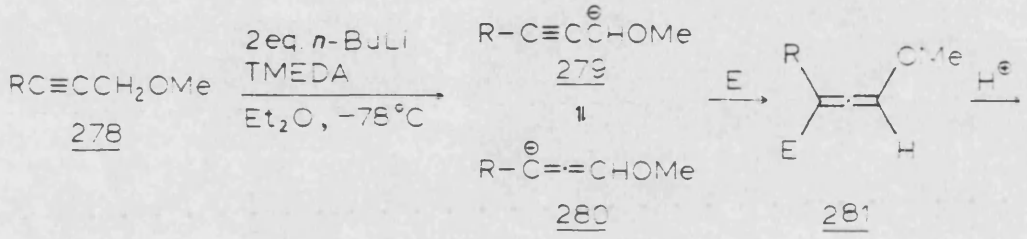
Scheme **95**. The approach above extends the carbon chain from C-1 and C-3 of the enone unit using umpolung to create d^1 and d^3 centres, and corresponds to scheme **B**, p. 4.

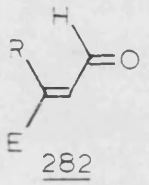
Martin *et al.*[193a] used methoxyallene 267 in reaction with triphenylphosphonium bromide to afford 3-methoxy-2-propenyltriphenylphosphonium bromide 273 in 68% yield. The phosphorane 273 was deprotonated with butyl lithium to give 3-methoxyallylidene triphenylphosphorane[193b] 274 which readily reacted with simple carbonyl compounds 275 to give the 1-methoxy-1,3-butadiene derivatives 276. Hydrolysis of 276 gave (E)-β- substituted acrolein derivatives 277 (Scheme 96).



Scheme 96

Leroux *et al.*[194] reacted several reagents known to be hard electrophiles with the equilibrium anionic mixture 279 and 280, obtained on metallation of the propargylic ether 278.[195] Reaction took place at the sp^2 anion of the allenic component, this negatively-charged centre believed to have a hard character. The substituted allenes formed[196] can be hydrolysed to β- substituted enones 282 (Scheme 97).



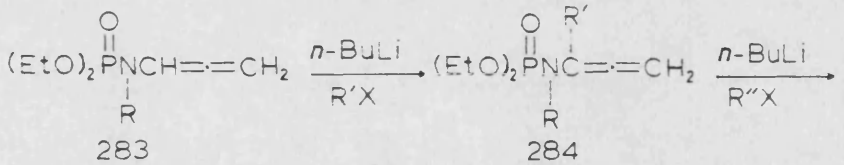


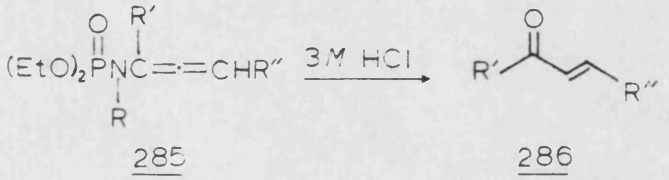
282

E	Yield 281 (%)
TMSCl	100
Me_2SO_4	80
Et_2SO_4	100

Scheme 97. R = C_5H_{11} .

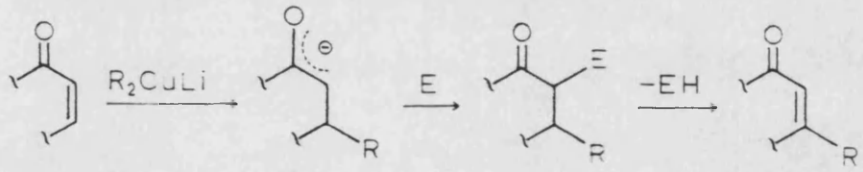
Corbel *et al.*[197] found that the *N*-allenyl phosphoramide derivatives[198] 283, prepared from the corresponding terminal acetylenes, could be sequentially metallated at C-1 and C-3, to afford (E)-1,3-disubstituted propenones 286 after hydrolysis (Scheme 98).





Scheme 98. R = Me, Et, $PhCH_2$.

In a similar approach to that outlined in Scheme 40 for α-functionalisation, conjugate addition reactions between enones and lithium organocuprates produce intermediate enolate anions which can be trapped with a variety of C-alkylating non-carbon electrophiles. These can be eliminated to transform the enones 287 into β- substituted derivatives 288 in a regiospecific manner[199] (Scheme 99). A procedure is known which effects the same conversion from an O-alkylating non-carbon electrophile.[200]



287 288

Scheme 99. E = PhSeX, PhSX, MeSOCl, Me_2S_2, Ph_2S_2.

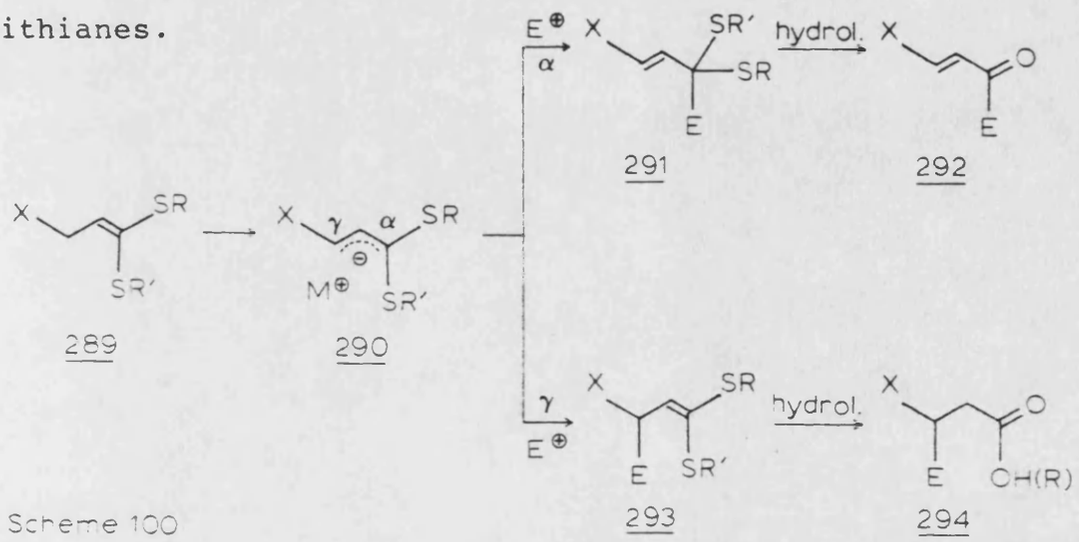
RESULTS AND DISCUSSIONS

2. RESULTS AND DISCUSSION

2.1 Introduction

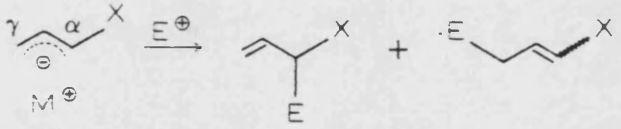
The preceding sections illustrated the use of masked acrylate anion equivalents in the formation of C-C bonds as a powerful strategy in the development of new synthetic methods. Before proceeding directly to a discussion of the interesting transformations which we were able to elicit from appropriately functionalised ketene dithioacetals [201], it is useful to mention some important points concerning the general behaviour of these bissulphur-substituted systems **289** in terms of their ambident allylic reactivity upon metallation.

The products of ketene dithioacetal chemistry clearly reveal the use of these compounds as both masked α,β - unsaturated acyl anion equivalents [202] **291** via α - alkylation, and masked β - propionate anion equivalents [203] **293** via γ - alkylation (Scheme 100). This reactivity pattern is intrinsic to the innate chemical character of these compounds, and demonstrates the umpolung reactivity of carbonyl compounds that for quite a long time seemed fashionably synonymous solely with the use of 1,3-dithianes.



Scheme 100

However, the control of regioselectivity of electrophilic attack at these ambident anions is crucial to their synthetic utility as reversed reactivity equivalents. The factors known to influence regioselectivity in the reactions of heteroatom substituted allylic anions [204] **295**, and resonance - stabilised enolates [205] have been investigated and well documented [206] (Scheme 101). These factors - nature of the heteroatom [207-217](X), substituent on the heteroatom, substituent on the allylic system, nature of the conjugated system, nature of the electrophile [218] (E^+), counterion [219] (M^+), and solvation [211a,f] - will also modify, each to a greater or lesser extent, the regiochemical tendencies of ketene dithioacetalides **290**; these anions effectively differing from **295** only in that they provide products at different oxidation levels upon hydrolysis. Indeed, although the route towards compounds

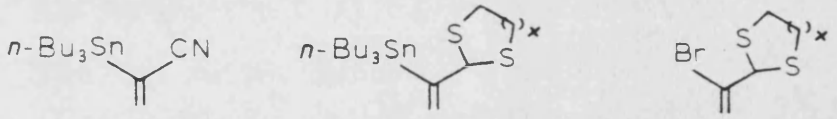


295

Scheme 101. X = R[207], OR[208], $OSiR_3$[209], OTHP[210], SR[211], SLi[212], SOR[213], SiR_3[214], SeR[215], NR_2[216], BR_2[217].

291 and **292** has been sufficiently demonstrated [220], development of the alternative role has largely emerged in conjunction with studies on the effect of solvent, counterion, etc. on the α/γ reactivity of **290** [221].

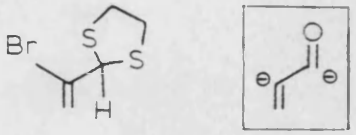
Our interest in the area of anion equivalents in general was focused upon ways in which we could synthetically develop an α-haloacrolein into a useable synthon. Our studies on ketene dithioacetals in particular were initiated by our failure to synthesize **297** from **296**[222], and by problems associated with the synthesis [223] and metallation [224] of **298**.



296 297 x = 1,2 298

2.2. The Synthesis of 1,1,3-Tris(phenylthio)-1-propene and its use as a β- lithioacrylate equivalent.

Our initial objective was to explore the possibility of establishing an operational equivalency between the vinyldithiolane **298** (x=1), and what we believed might be a novel propenone 1,2 -dianion[225] **299** via successive metallation at C-2 and C-Br, or vice versa.

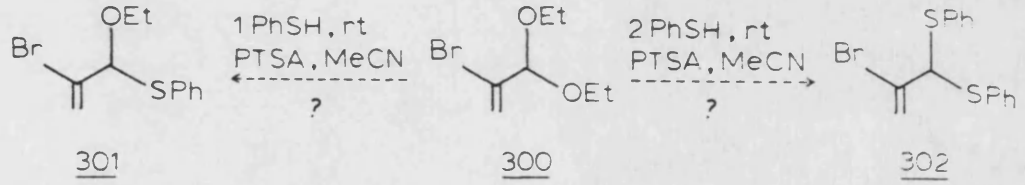


298 (x=1) 299

That this was not realised could possibly be attributed to competing processes: C-4 metallation[224], allene formation via C-2 proton abstraction (LDA), and the possibility of indiscriminate anion generation with n-butyllithium at the reaction temperature employed (-78°C). Parenthetically, we

might note that some time after we had turned our attention to 'sulphur-separated' systems, control of reaction temperature and choice of base reagent were shown in concert to effect the halogen-metal exchange stage of the strategy proposed above, for a similar (cyclic) system [226].

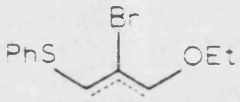
We then briefly examined the reaction of 2- bromo-1,1-diethoxy -2-propene[227] (**300**) with both one and two equivalents of thiophenol in attempts to produce, respectively, the hemithioacetal[228] **301**, and the S,S- acetal **302** in which the sulphur atoms are not incorporated into a ring structure[229] (Scheme 102).



301 300 302

Scheme 102. Use of $BF_3 \cdot OEt_2 / CH_2Cl_2$ achieved the same result (see text), but reaction was cleaner overall.

In both cases, reaction was complete after 30 minutes, (as judged by t.l.c.) and NMR confirmed the same structure to have been formed in both instances[230]. The product was identified as the result of a conjugate addition of the soft [231] heteronucleophile to the vinylic terminal carbon atom of the intermediate α,β - unsaturated oxonium cation, although the position of the C=C in **303** was not confirmed.

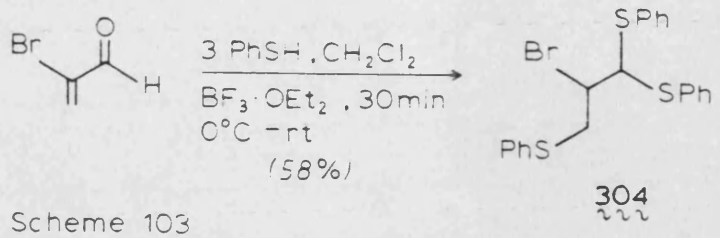


303

The alkylation of **303** was not studied in any detail, and instead, similar conditions were applied to the unprotected α - bromoacrolein[232].

Treatment of a dichloromethane solution of α-bromoacrolein and 2.5 equivalents of thiophenol with boron trifluoride etherate [233] produced an opaque yellow solution which was subjected to an aqueous base work-up procedure after 30 minutes stirring at ambient temperature. Unfortunately, evaporative distillation at reduced pressure resulted in decomposition of the single product formed. However, the reaction was quite reproducible, and for characterisation purposes it was thought that purification would be adequately effected chromatographically. Even rapid elution of the component through silica gel could not prevent some measure of degeneration, but any reduction in sample quality was negligible. Subsequent spectral analysis revealed an absence of any distinctive features attributable to **302**, and our previous experience concerning the behaviour of thiols with C-3 unsubstituted or unhindered enone systems[234] allowed us to conclude that 2-bromo -1,1,3-tris(phenylthio)propane(**304**) had been formed via initial 1,4- addition of thiophenol. When the stoichiometry of the reaction was adjusted accordingly, and three equivalents of thiophenol employed, all of the starting aldehyde was

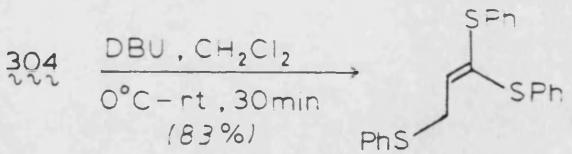
cleanly consumed, and the same product, **304**, was isolated (Scheme 103).



304

Scheme 103

The synthetic utility of **304**, formed more fortuitously than by design, was immediately recognised as offering an operational simplicity free of the problems that might overshadow the use of **301** and **302** as synthetically viable reagents. A retrospective examination reveals some common features between **304** and 1,3-bis (methylthio)-2- methoxy propane[149a,b] (**173**) in that reaction with base (regiospecifically) generates a sulphur-stabilised anion as the intermediate, eliminating a C-2 substituent[235] and allowing access to 1,1,3-tris(phenylthio)-1-propene (**305**), itself a close relative of the Cohen compound **183** (Scheme 104).



304 **305**

Scheme 104

The 2- bromopropane **304** was exposed to a number of basic conditions (Et_3N, pyridine, DBU, ^tBuOK, K_2CO_3, $Me_2NC(NH)NMe_2$) in attempts to produce **305** efficiently. In all cases, reaction was conducted using 10% excess of base, and varying degrees of success were apparent with all but

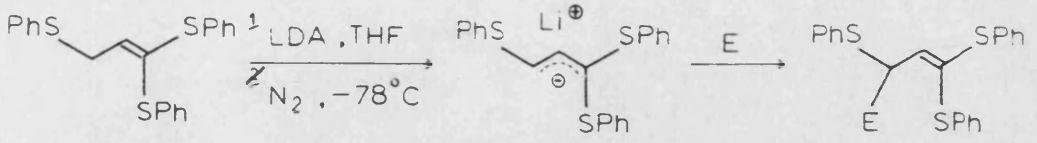
Et_3N and pyridine. However, only DBU could sustain rapid, near-quantitive conversion to **305** when the dehydrobromination reaction was scaled up from 0.11mmol(40mg) of **304**. In subsequent experiments, given the somewhat labile nature of **304**, it was more convenient to prepare **305** in a one-pot procedure in 83% overall yield without additionally interrupting the reaction sequence to purify an essentially clean intermediate. Although **305** was subjected to evaporative distillation, purification was readily and best effected by filtration through silica gel.

The deprotonation and alkylation of the ketene dithioacetal **305** were then investigated. Treatment of **305** with 1.1 equivalents of LDA[236] in THF at -78°C resulted in a dark green solution which was allowed to warm to -40°C over ca. 1.5hr. The solution was maintained at this temperature for 30 minutes, after which time the anion solution was recooled to -78°C and treated with a variety of electrophilic reagents to afford the γ-alkylated products **307** exclusively[237] (Table 1). Ordinarily the reaction mixture was allowed to warm to ambient temperature before terminating the reaction with aqueous ammonium chloride solution. However, we found that in the reaction of the ketene dithioacetalide **306** with cyclohexanone (entry m), although reaction took place fairly readily at - 78°C, a retro-aldol reaction[240] occurred at higher temperatures, and only **305** was recovered. In a subsequent experiment therefore the hydroxyalkylation reaction was quenched with

ammonium chloride solution after ca. 30 minutes at -78°C, to afford an excellent yield of **307**m. This slight modification was employed for cyclopentanone (entry n), ethyl chloroformate (entry u), and carbon dioxide (entry v), although no concomitant starting material regeneration was observed in the reactions of benzaldehyde (entry h) or 4-methylpent-3-enal[241] (entry s) on warming.

TABLE 1

Summary of results obtained in the alkylation[238] of 1,1,3 -tris(phenylthio)-1-propene (**305**)



305 306 307

Entry	Electrophile	E in **307**	Yield (%)[a]
a	CH_3I	CH_3	82[b]
b	$(CH_3O)_2SO_2$	CH_3	81[b]
c	$(CH_3)_3SiCl$	$Si(CH_3)_3$	95
d	D_2O	D	77
e	H_2O	H	86[c]
f	$PhCH_2Br$	CH_2Ph	87
g	$PhCH_2Br$/HMPA	CH_2Ph	85[d]
h	PhCHO	CH(OH)Ph	70[e]
i	$CH_2=CHCH_2Br$	$CH_2CH=CH_2$	82
j	CH_3CH_2I	CH_2CH_3	96
k	$CH_2=CHCH_2CH_2Br$	$CH_2CH_2CH=CH_2$	74
l	$CH_3CH(Br)CH_3$	$CH(CH_3)_2$	42[f]
m	cyclohexanone	$C(OH)CH_2)_4CH_2$	93
n	**cyclopentanone**	$C(OH)(CH_2)_3CH_2$	77[g]
o	**ethylene oxide**	CH_2CH_2OH	72
p	$Br(CH_2)_4Cl$	$CH_2(CH_2)_3Cl$	80
q	MeSSMe	SMe	76[h]
r	PhSSPh	SPh	76

cont..../

TABLE 1

Summary of results obtained in the alkylation[238] of 1,1,3 -tris(phenylthio)-1-propene (**305**)

Entry	Electrophile	E in **307**	Yield (%)[a]
s	$Me_2C{=}CHCH_2CHO$	$CH(OH)CH_2CH{=}CMe_2$	85[i,e]
t	$CH{\equiv}CCH_2Br$	$CH_2C{\equiv}CH$	61[j]
u	$ClCO_2Et$	CO_2Et	72[j]
v	CO_2/H_3O^+	CO_2H	81[j]

a Isolated yields after chromotography on silica gel.

b This compound has been previously reported see ref.[229].).

c No isomerization to the vinyl sulphide **309** was detected.

d The use of 3 equiv HMPA had no effect on the regioselectivity: see refs.[221b] and [220b].

e Obtained as a 2:3 mixture of diastereoisomers.

f Overall reaction time longer that for primary alkyl halides hence yield loss due to competing side reactions.

g 90%, corrected for recovered **305**.

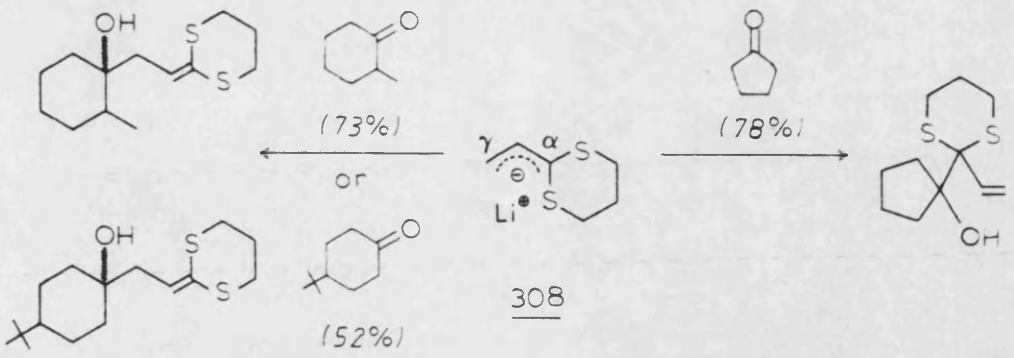
h 84%, correct for recovered **305**.

i Yield corrected for recovered **305**.

j See ref. [239].

The formation of these γ-alkylated regioisomers was best checked by NMR. Complete disappearance of the vinyl proton (δ6.06) of **305** was attended by the appearance of a doublet (δ 6.04-6.38 depending upon the specific adduct), and this regiochemical assignment placed a consistent value on the coupling of the vinyl-allyl-proton pair of 10-11 Hz, this being in agreement with literature values on similar systems[242]. In addition, it was realised that ^{13}C data would be decisive in distinguishing the ketene dithioacetal adducts[243] **307** from the isomeric vinyl sulphides, as the former would be expected to exhibit a resonance due to the methine carbon atom in a region of the spectrum relatively free of other signals. This was indeed the case, and values of δ 38.63 - 62.46 were observed for the tertiary carbon centre.

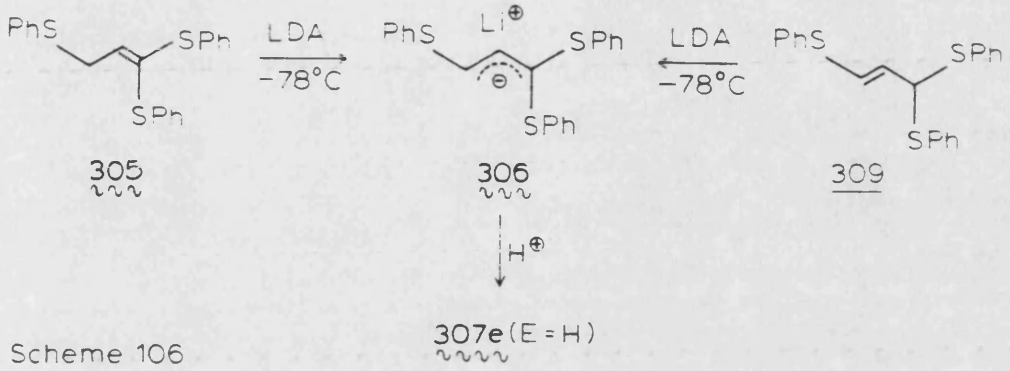
Several entries in Table 1 merit further consideration. Kozikowski *et al.*[221a] showed that in reaction with the anion derived from 2- ethylidene - 1,3- dithiane **308**, cyclopentanone reacted exclusively at the "harder" α - site, the site of higher electron density, whereas cyclohexanone derivatives were observed to react solely at the "softer" γ - site[221c] (Scheme 105), a result arising from correlation of the relative "hardness" of the carbonyl centres with the ambident anion. Coupled with the observation that alkyl halides and carbonyl compounds often take different courses in reaction with ambident anions[218],



Scheme 105

it is interesting to note that a distinction between the two classes is not observed with **305**. The interesting points that are raised by these experimental results are more fully discussed in the next section (Section 2.3).

The allylic anion arising from deprotonation of the ketene dithioacetal **305** reprotonates exclusively at the γ-position when treated with distilled water at -78°C (entry e). The isomeric vinyl sulphide, 1,3,3-tris(phenylthio)-1-propene (**309**), prepared by McKervey *et al.*,[244] was deprotonated with LDA at -78°C and aqueous NH_4Cl solution was added once the reaction mixture reached -40°C. The quantitative (as judged by t.l.c.) formation of **305** enforces the observation that the route to **306** does not affect the orientation of alkylation[221c] (Scheme 106).

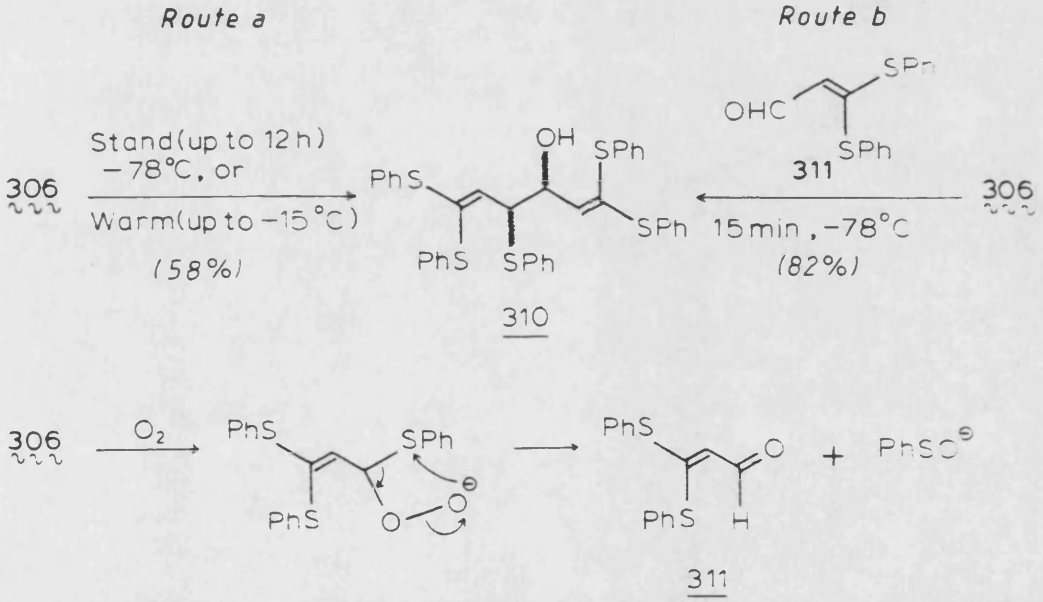


Scheme 106

The dialkylation of **305** was also briefly examined. 1,1,3-Tris(phenylthio)-1-butene (**307a**) was subjected to the same alkylation reaction conditions as those employed to secure the results in Table 1, and iodomethane was chosen as the electrophilic probe. Unfortunately, t.l.c. and ^{1}H NMR revealed starting material only, and it is believed that **307a**, and therefore presumably the higher homologues are too sterically encumbered to allow close enough approach of the base for removal of an allylic proton a second time (see Section 2.4.).

A particularly interesting finding that deserves mention, owes more to the alkylation procedure itself for its revelation than to any of the individual results that were subsequently obtained. Complete formation of the lithiated species **306** was ensured by allowing the reaction mixture to warm to -40°C over a period of up to 2 hours prior to introducing a particular electrophilic reagent[245]. This routine operation, common to all entries in Table 1,

was believed to be responsible for the appearance, in all cases, of a trace component at Rf 0.38 (1:5 ethyl acetate/petroleum). Subsequent spectral analyses[239] led one of our co-workers, D. M. Hodgson, to propose a diastereoisomeric mixture of alcohol **310** as the result of an oxidative coupling reaction[246] involving the trapping of oxygen by **306** to form 3,3-bis(phenylthio)acrolein[247] (**311**). This mode of reactivity could be made to predominate as shown in Scheme 107 (route a), and was confirmed independently in route b.



Scheme 107. Rearrangement to 311 may take place intermolecularly, not intramolecularly as shown.

1,1,3-Tris(phenylthio)-1-propene(**305**) and the adducts **307** contain both a protected carboxylic acid (or ester), and a group at the γ- position (PhS) that may be eliminated to introduce α,β-unsaturation. Hydrolysis of the ketene dithioacetal moiety and elimination of thiophenol from **307** therefore provides access to a generalised β-lithioacrylate

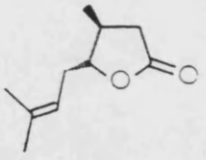
equivalent that could, in addition, lead directly to γ-mono- or γ,γ- disubstituted butenolide systems [248] **116** with those adducts possessing an internal hydroxyl function (Scheme 108).

307

307 h,m,n,o,s 116

Scheme 108

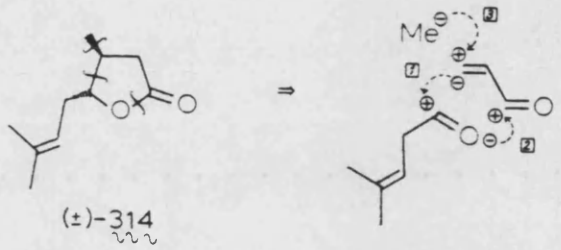
At about the same time a lot of synthetic interest was generated regarding a C_{10} γ-lactone [249] of terpene origin [250], eldanolide (**314**)[251]; isolated from the wing glands of the male African sugar cane borer, Eldana saccharina (Wlk.).[252]



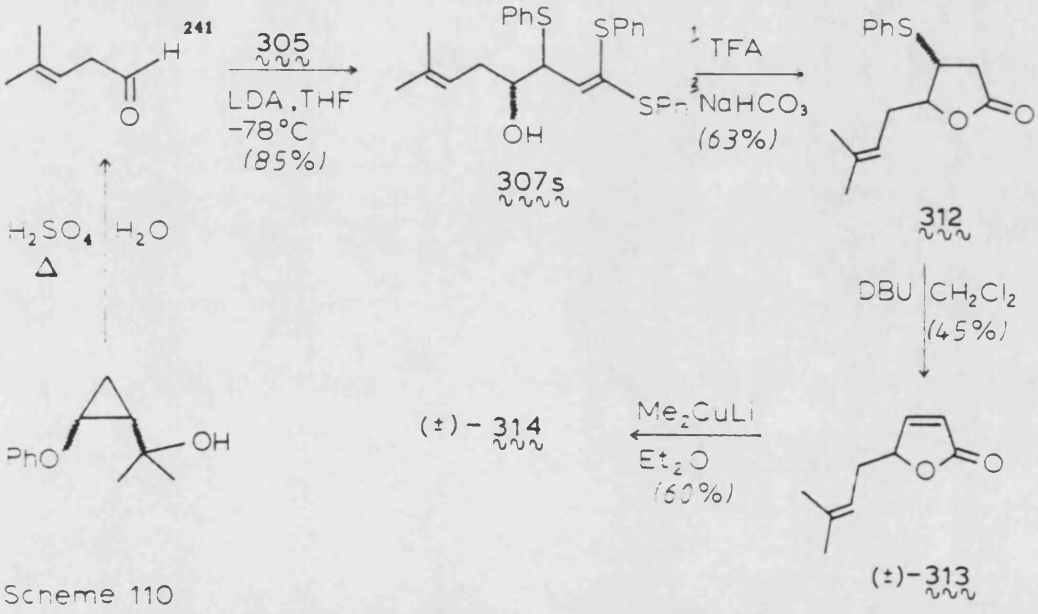
314

We realised that this agronomically important [253] attractant pheromone would prove ideal for an exemplary use of **305** in a short, albeit racemic, synthesis. The ketene dithioacetal **305** would provide the backbone of the lactone ring in reaction with the appropriate carbonyl substrate, establishing the C-4 allylic "prenyl" (3-methyl-2-buten-1-yl) side chain. By virtue of thiophenol elimination, the resulting butenolide would be set up for introduction of the

C-3 methyl substituent. In this way both the abnormal donor and normal acceptor C-3 reactivities of a propenone system could be made to act in succession. The disconnections envisioned for this strategy are depicted in Scheme 109,[254] and our route to (±)- eldanolide shown in Scheme 110.



Scheme 109



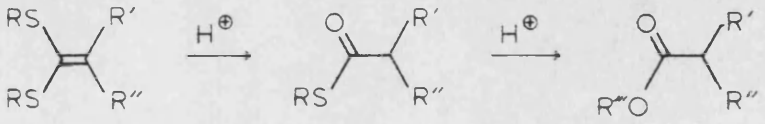
Scheme 110

The formation of 4-methylpent-3-enal (28%) resulted in contamination with the conjugated isomer, 4-methylpent-2-enal (9%), the latter arising under the acidic conditions required for the phenoxycyclopropane derivative ring-opening reaction. Alkylation of **305** with the β,γ-unsaturated aldehyde was undertaken without further attempted exclusion of the α,β- unsaturated isomer and reaction took place

readily at -78°C to give alcohol **307s** as a mixture of diastereoisomers. ^{1}H NMR analysis revealed only those diastereoisomers arising from reaction with the β,γ-unsaturated aldehyde; no reaction with the α,β- unsaturated aldehyde was noted.[255]

Elimination of the bissulphur functionality at the double bond was first attempted under the classical hydrolytic conditions using the thiophilic species Hg^{2+} and Ag^+ in aqueous acetonitrile or aqueous THF.[256] Infra-red spectroscopy was chosen as the diagnostic technique whereby production of a saturated γ-lactone could be most easily detected. Unfortunately, this procedure was unsuccessful, and it was recognised that the presence of the γ-phenylthio group might cause problems by complexing to the metal species as well. A superior procedure would be one which would differentiate between the phenylthio groups attached to the differently - hybridised carbon centres.

Hydrolysis of sulphur-separated ketene dithioacetals has been previously achieved with acid[257], the intermediate compound on the route to the free carboxylic acid or ester derivative being the thiol carboxy derivative[258] **315** (Scheme 111).

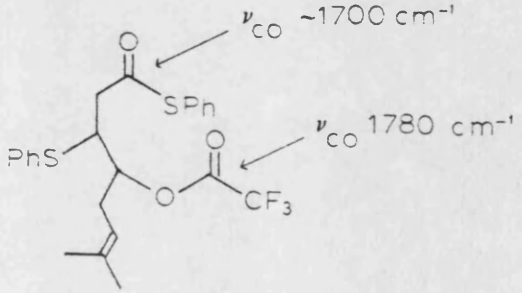


315

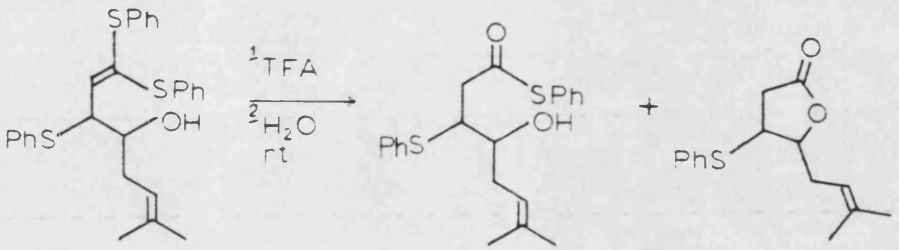
Scheme 111

The reactivity of **315** towards oxygen-(and nitrogen) nucleophiles [259] would result in the intramolecular transesterification of the acyl sulphide moiety, the internal hydroxyl group effecting ring-closure to the lactone in the process. This is effectively an acylation reaction on the hydroxyl oxygen, for which thiol esters often show an enhanced or more specific reactivity as compared with their oxygen analogues.[260] Use of TFA for the hydrolysis of **307s** would carry the reaction to the corresponding acyl sulphide stage, but hydrolysis to carboxylic acid derivatives is known not to occur under these conditions.[261]

Treatment of **307s** with 9 equivalents of TFA[262] at ambient temperature in dichloromethane, and addition of water 20 minutes later produced a single reaction component (by t.l.c.) in a procedure that was cleaner than those in which Hg^{2+} or Ag^{+} had participated. Infra-red analysis was initially misinterpreted as indicative of incomplete conversion to **312** (Scheme 112). However, simple t.l.c. evidence and the persistence of the characteristic IR absorption due to the S-aryl carboxylate strongly intimated that the hydroxyl function was acetylated before the acyl sulphide was formed, so that an acylic structure, **317**, resulted.



317



307s — 316 — 312

	ν_{CO} (cm^{-1})	ν_{CO} (cm^{-1})
expected:	1695-1680[261]	1780-1760
observed:	~1700	1780 (plus ν_{O-H})

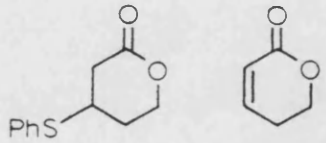
Scheme 112

A molecular ion peak at m/z 468 was evident upon mass spectral analysis, and subsequent fragment ions were consistent with loss of hydrogen fluoride, phenylthio and trifluoroacetate radicals. Treatment of **317** with $NaHCO_3/H_2O$/MeOH at ambient temperature cleaved the ester linkage initiating cyclization to **312**, accompanied by the odour of thiophenol which became a reliable olfactory signal in these reactions.

Elimination of the γ-PhS group was achieved with DBU[263] to afford the known butenolide derivative, (±)- **313**, the common key precursor in a number of published routes.[178,237,252e,f,j,n.]

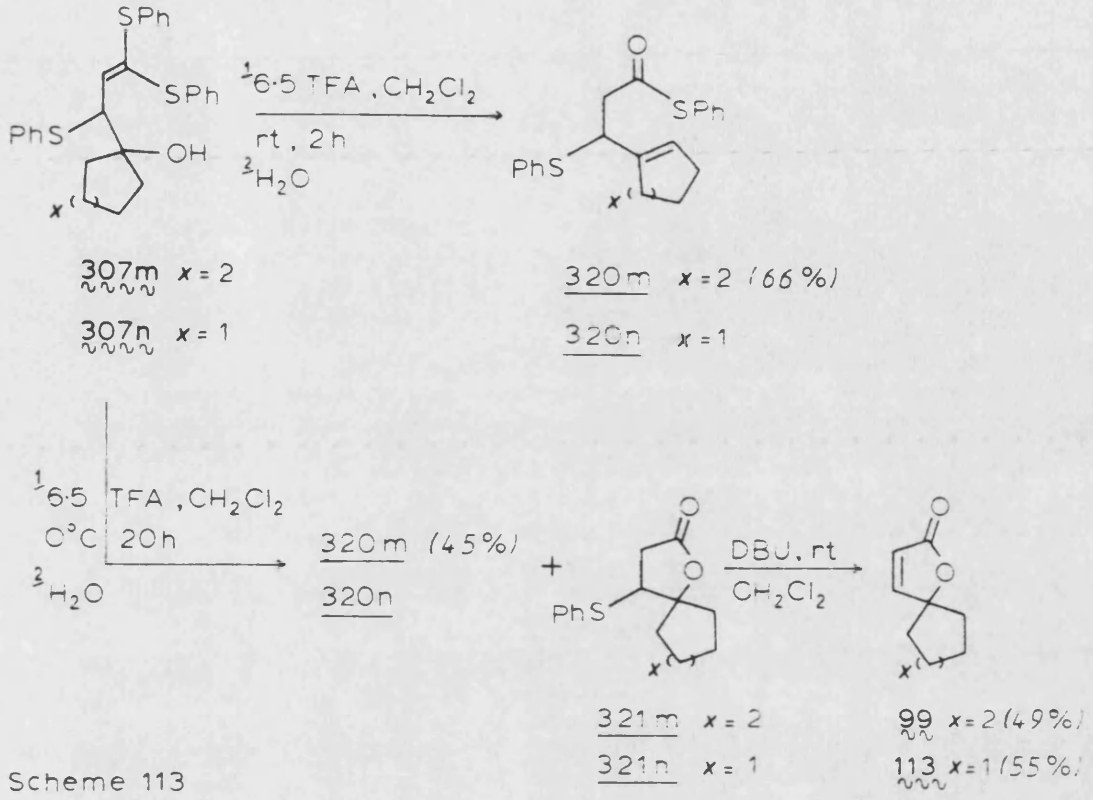
The route to (±)- eldanolide was completed by a stereospecific Michael addition of lithium dimethylcuprate.[252 d-f,264-5] Indeed, conjugate additions of nucleophiles to γ- substituted α,β- butenolides are reported to occur in a highly stereocontrolled manner to give trans -3,4- disubstituted butyrolactones[265].

The conversion of hydroxyalkylated adducts to the corresponding α,β-unsaturated lactones was used definitively to confirm the regiochemical assignment. TFA-induced hydrolysis of **307o** formed the intermediate 4-(phenylthio)tetrahydro-2-pyranone(**318**) which was not fully characterised[266] but treated with DBU to remove the β-phenylthio group to give 5,6- dihydro -2H-pyran-2-one[267](**319**).



318 319

The corresponding hydrolyses of adducts **307m** and **n** were more problematic. Unlike the previous adducts **307s** and **o**, which feature, respectively, secondary and primary hydroxyl functions, the presence of tertiary alcohol centres resulted mainly in E1 elimination of water to the relatively stable carbonium ions. Loss of a ring proton formed the cyclohexene and cyclopentene derivatives, but to a certain extent the reaction was temperature dependent (Scheme 113), and our study was mainly confined to the cyclohexanol adduct **307m**.

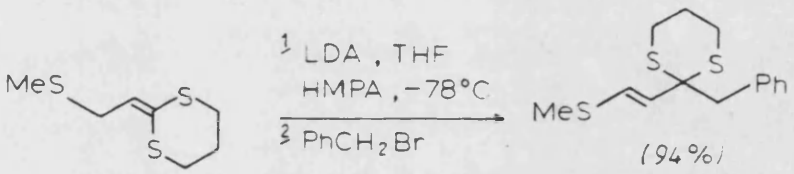


Scheme 113

Once obtained, the saturated spirolactones[268] were treated with DBU to form the corresponding α,β-unsaturated spirolactones **99** and **113** for which the spectral data were consistent with the assigned structures [113], and which had the peculiar property of smelling of coconut oil (cf. γ-pelargonolactone **6**). When **307m** was treated with acetic acid at ambient temperature, quantitative conversion to **321m** was observed after standing for 40 days. Formation of **99** was thereby effected in 50% overall yield.

2.3 1,1,3-Trissulphur substituted propene systems: The effect of altering the heteroatom substituents on the regiochemistry of alkylation.

The dramatic and, for alkyl halides,[163e] unusual γ-regioselectivity exhibited by **305** (Table 1) directed our investigations towards other 1,1,3-trissulphur substituted propenes incorporating different heteroatom substituents. The study was additionally prompted by the α-exclusive alkylating behaviour exhibited by compound **322**,[220b] a system which on casual inspection closely resembles **305** (Scheme 114).



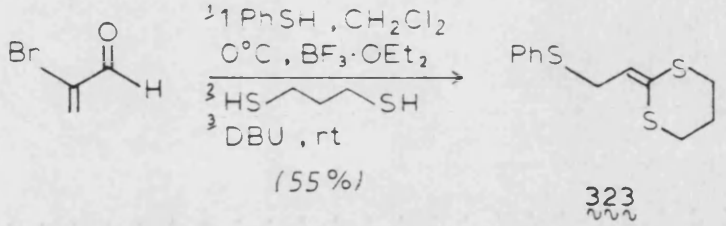
322

Scheme 114 . See Table 5 , entry b .

Application of the methodology used to synthesize **305** also simultaneously explored the generality and convenience of our ketene dithioacetal synthesis.[269]

We began by examining the behaviour of 2-(2-phenylthioethylidene)-1,3-dithiane[269b] (**323**), in which the substituents and steric environment around the α- carbon atom were altered, but retaining the bulky phenylthio group at C-3. This molecule also provided a structure intermediate between **305** and **322** (the alkylation of **322** was also investigated and its behaviour corroborated - see Table

5). The procedure employed to synthesize **323** is shown in Scheme 115, and confirmed the course of the present heteronucleophilic attack on an enone system.[233,234]



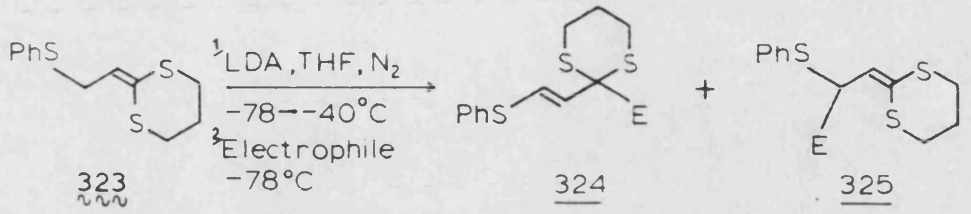
323

Scheme 115. Ref. *269b* reports a yield of 85% for **323** although the overall route is longer.

The alkylation procedure followed was the same as that employed in the reactions of **305**, and the results are tabulated below:

TABLE 2

Summary of results obtained in the alkylation of 2-(2-phenylthioethylidene)-1,3-dithiane[a] (**323**).



323 324 325

Entry	Electrophile[f]	Ratio 324(α):325(γ)		Yield (%)[b] 324+325
a	$(CH_3)_3SiCl$	77	23	44[c]
b	$PhCH_2Br$	57	43	44
c	$PhCH_2Br$/HMPA	50	50[d]	44[c]
d	cyclohexanone	62[e]	38	66[c]

[a] **323** was a low melting solid which gradually decomposed on storage under N_2, even at -15°C.

[b] Isolated yields after chromatography on silica gel.

[c] Yield corrected for recovered **323**.

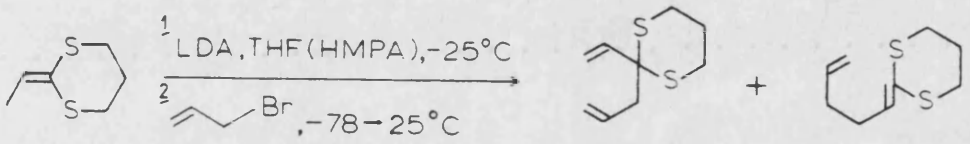
[d] Determined by 60 MHz ^1H NMR analysis.

[e] **324d** was a low melting solid.

[f] For E in **324/325**, see Table 1.

It is apparent from Table 2 that there is little regioselective discrimination between cyclohexanone and alkyl halides. This suggests that the rule of thumb noted in references 209(b) and 218 is just that, and does not apply rigidly in all circumstances although deviations are

normally attributed to steric effects. On a purely steric argument, however, the retention of a γ- phenylthio group should direct electrophiles to reaction at the α-carbon atom, as it is known [221d] that the regioselectivity for α-alkylation (specifically, allylation) is greater in the cyclic dithiane than in the acyclic analogues (Scheme 116).

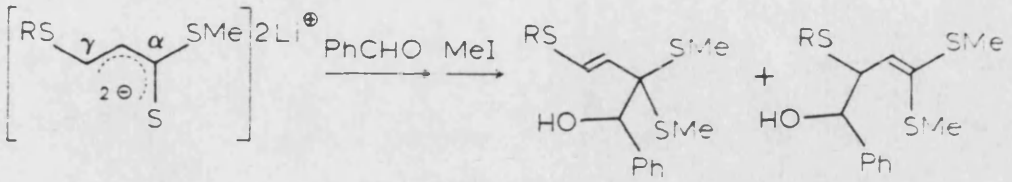


	α	γ
with HMPA	94	6
without HMPA	88	12

Scheme 116

Ziegler [221b,d] also noted that the regioselectivity of alkylation of ketene dithioacetalides was not affected by the addition of HMPA even though it is known that HMPA selectively solvates metal cations [270]. This is borne out by entries b and c. However, more importantly from a quantitative viewpoint, it is apparent that in contrast to Scheme 114, the γ-regioisomers **325** are formed in significant amounts, and may on occasion (entry c) constitute up to 50% of the isolated product yield. Recently, Beslin et al [271] alluded to the possibility that incorporation of a γ-phenylthio group in a novel ambident dianion leads to non-coincidence for the largest HOMO coefficient on the γ-site and the highest electron π charge density on the α-site (Scheme 117). This manifested itself as α-selectivity in the case of aldehyde additions; clearly, these initial

studies indicate that the balance between steric and electronic effects in these systems is a fine one.

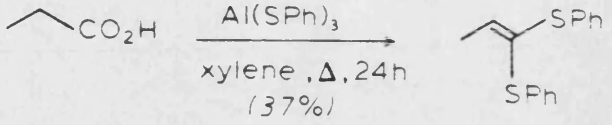


	α	γ
R = Me	50	50
R = Ph	75	25

Scheme 117

In our previous communication[237] concerning the regioselective alkylation of **305** we had stated that "incorporation of a γ-phenylthio group ...directs both 'hard' and 'soft' electrophiles to the γ-site exclusively". We reasoned that the alkylation behaviour of 1,1-bis(phenylthio)-1- propene[272] (**326**) would best demonstrate this empirically. Specifically, we wanted to determine whether the exclusive γ-alkylation seen previously was genuinely due to direct steric hindrance about C-1, the α-phenylthio groups being in close proximity, or whether by virtue of the presence of a bulky γ-phenylthio group, the two α-substituents are forced together thereby indirectly conferring a restricted approach to eletrophiles at C-1.

Unable to use our procedure for the synthesis of **326**, we turned to the literature method described by Cohen et al.[229] involving a reaction of propionic acid and aluminium thiophenoxide[273] (Scheme 118).



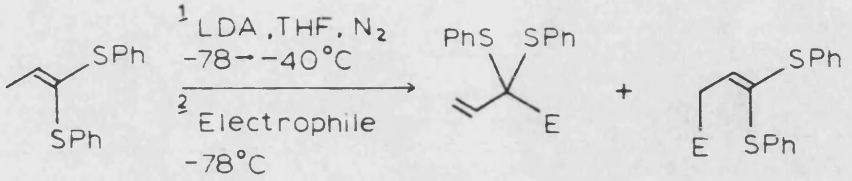
326

Scheme 118. Cohen *et al.*[229] report a yield of 56%; Heves *et al.*[272b] report a yield of 72%.

The alkylation procedure employed also involved a 30 minute period of stirring at -40°C before reaction at -78°C, and the results of our study are outlined in Table 3.

TABLE 3

Reaction of metallated 1,1-bis (phenylthio)-1-propene (**326**) with various electrophiles



326 327 328

Entry	Electrophile[f]	Ratio 327(α):328(γ)		Yield (%)[a] 328
a	cyclohexanone	0	100	75[b]
b	$PhCH_2Br$	0	100	64[c]
c	$PhCH_2Br$/HMPA	0	100	-[d]
d	PhSSPh	0	100	31[e]
e	MeSSMe	0	100	48
f	$(CH_3)_3SiCl$	0	100	66
g	MeOH	0	100	-[d]

a Isolated yields after chromatography on silica gel.

b 95%, corrected for recovered **326**.

c Formed crystals at -15°C which melted at rt.

d Product detected (60MHz ^1H NMR) but not purified.

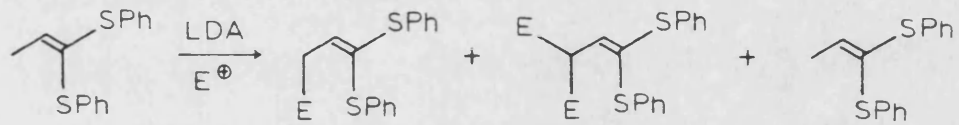
e 37%, corrected for recovered **326**.

f For E in **328**, see Table 1.

The reactions as a whole were not as clean as those involving **305**, and there was a further point of interest. In some cases, the initially-formed mono-alkylated products were themselves likely to undergo substitution reaction. The full extent of reaction for these entries is summarised in Table 4.

TABLE 4

Distribution of mono- and disubstituted products in the alkylation of **326**



326 328 329 326

Entry from Table 3	Electrophile[c]	Yield (%)[a] 328	329	326
d	PhSSPh	31	28	16
e	MeSSMe[b]	53	18	-

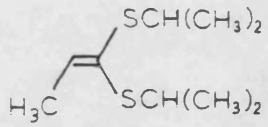
a Isolated yields after chromatography on silica gel.

b The result recorded in Table 3 represents an entry in which only a trace of **329** was formed.

c For E in **328/329**, see Table 1.

In view of the results compiled in Table 1, those presented in Table 3 are perhaps not so surprising. Ziegler

et al.[221d] in seeking to control the γ-alkylation of systems similar to **326** had, after all, already noted that a greater degree of γ-alkylation could be induced by employing heteroatom substituents with greater steric bulk. However, what is significant about our findings is the degree to which regioselective alkylation can be controlled or achieved with **326**. Rather than representing a "limiting case in terms of steric bulk" the diisopropyl ketene dithioacetal[221d] **330** (for which α/γ is at best only 1/1.3) appears mediocre by comparison. Although the tert-

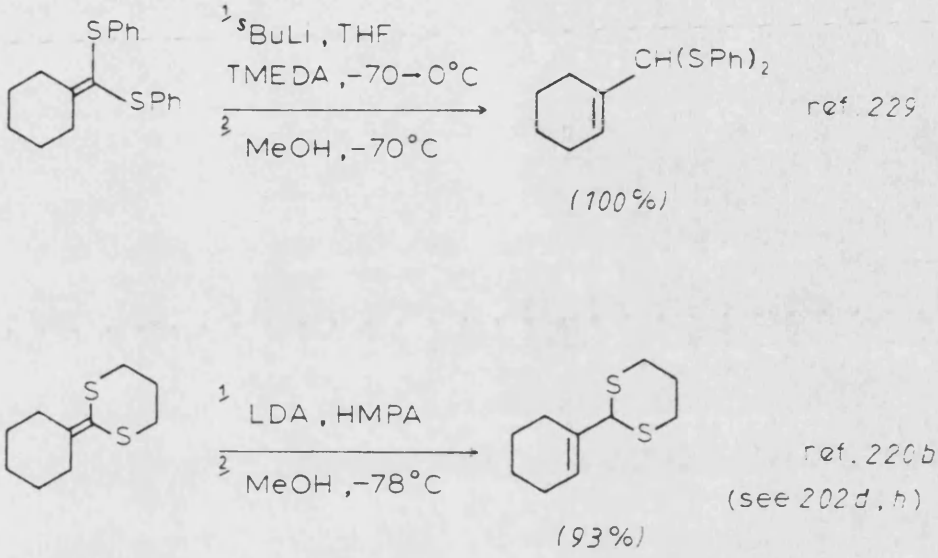


330

butyl analogues are not easily prepared, use of **326** would have provided Ziegler with a β-propionate anion equivalent without recourse to using cuprous salts.

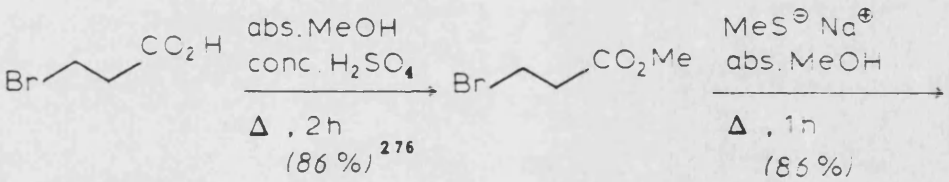
Although the results of Table 3 would seem quite clearly to resolve any steric vs. electronic argument for the behaviour of **306**, an interesting if somewhat speculative indication concerning the role of the γ-phenylthio group is provided by Table 4. Compound **328d**, arising from reaction with diphenyl disulphide, is more likely to form another anion [274] than that arising from reaction with dimethyl disulphide, and this says something about the relative acidities of the allylic protons in these structures. Interestingly, the following comparisons show α-protonation

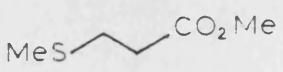
in a 1,1-bis(phenylthio)propene system to be a possibility (Scheme 119).



Scheme 119

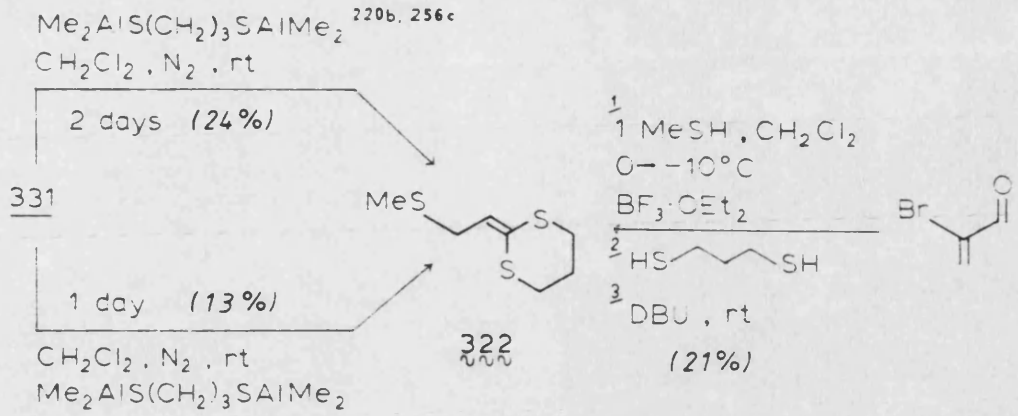
We next looked at the production and alkylation of systems wholly incorporating alkylthio substituents, and undertook to synthesize and metallate **322**. Three routes to **322** were attempted (Scheme 121), one employing α-bromoacrolein, and the others starting from methyl 3-methylthiopropionate[275] **331**, itself synthesized as shown in Scheme 120.





331

Scheme 120



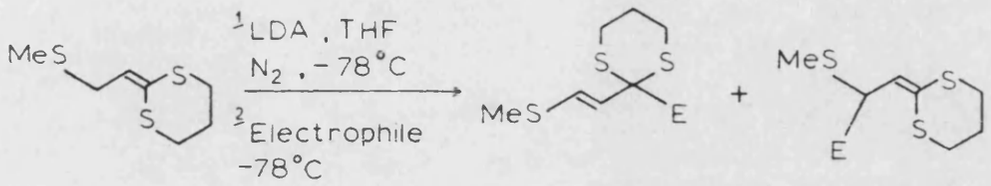
Scheme 121 .Corey *et al.*[220b] report 52% yield for 322.

Although both routes afforded comparably low yields of **322**, we decided to use the aluminium-based chemistry; the procedure involving α-bromoacrolein afforded product which was difficult to isolate from the other reaction components. Indeed, we had originally attempted the latter method with 3 equivalents of cyclohexanethiol, but even with the diethoxy acetal **300**, multi-component reaction mixtures were the result.

In contrast to the previously-employed procedures, the anion solutions were quenched with electrophilic reagents 30 minutes after anion generation at -78°C, and the results are summarised in Table 5.

TABLE 5

Reaction of metallated ketene dithioacetal **322** with various electrophiles.



322 332 333

Entry	Electrophile[g]	Ratio[a] 332(α):333(γ)		Yield (%)[b] 332+333
a	$(CH_3)_3SiCl$	100	0	50[c,d]
b	$PhCH_2Br$	100	0	34(lit.[220b]94)[f]
c	cyclohexanone	82	18	45[e]

a Determined by 60 MHz ^1H NMR analysis.

b Isolated yields after chromatography on silica gel.

c 62% yield when corrected for recovered 322.

d 332a was a low melting solid.

e Complete spectroscopic purity was difficult to achieve and physical characteristic IR, NMR, and MS anal. not determined.

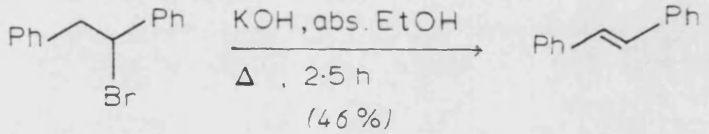
f Conducted by Corey et al. in the presence of HMPA.

g For E in **332/333**, see Table 1.

In our hands, both the synthesis and alkylation of **322** were inefficient operations[277]. This is, we believe, largely due to the instability of **322** and its alkylation

products: in parallel with **323**, a gradual discolouration and increase in viscosity was evident for **322** on storage under nitrogen, even at -15°C. When **322** was stored in a benzene matrix at -15°C, not only was the sample quality maintained, but reaction proceeded cleanly in fair to good yield (entry a).

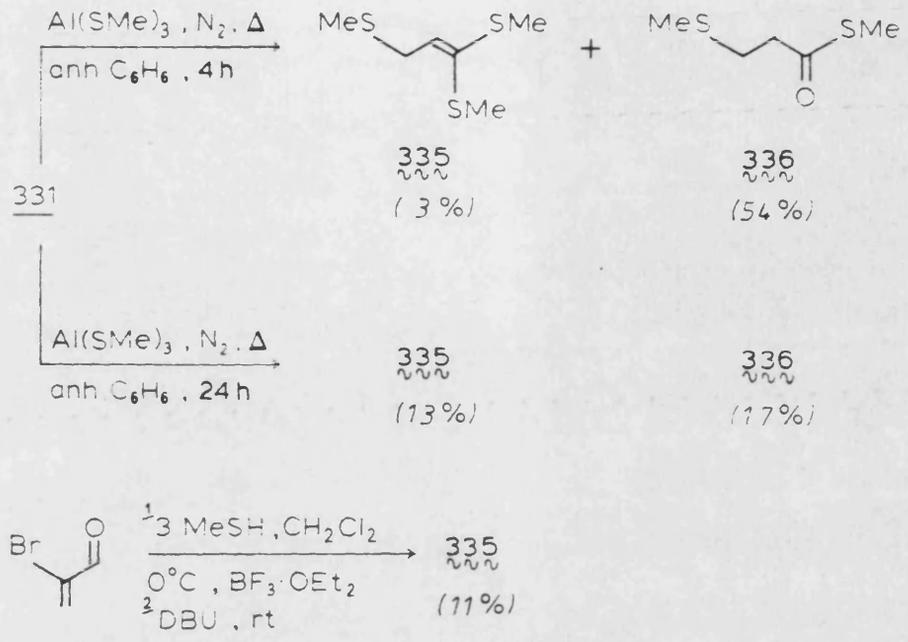
An interesting result to emerge from the benzylation of **322** (Table 5, entry b), and which may have contributed to the yield loss of **332b**, concerns the isolation of a colourless liquid in 64% yield. This compound was identified as 1-bromo-1,2-diphenylethane[278] (**334**), and this assignment was chemically confirmed as illustrated in Scheme 122.



334

Scheme 122. NMR, mp, and mmp corresponded to authentic *trans*-stilbene.

The synthesis of **335**, the methylthio analogue[279] of our parent ketene dithioacetal **305**, was also accomplished from methyl 3-methylthiopropionate (**311**). Although the alternative procedure from α-bromoacrolein afforded **335** in comparable yield, this preparative method was inferior to that employing **311** with respect to the overall cleanliness of reaction: distillation of the residue did not effect satisfactory analytical purity (Scheme 123).



Scheme 123

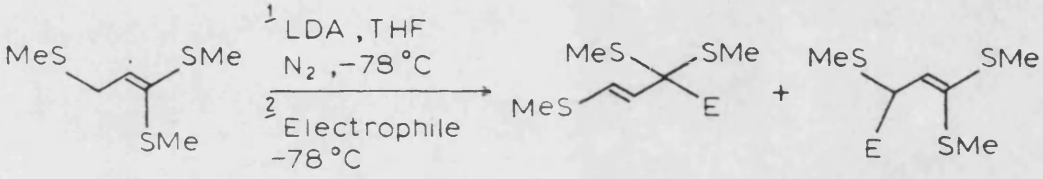
The reaction of aluminium thiophenoxide with saturated methyl esters is reported to yield the corresponding ketene dithioacetals in 89-100% after refluxing in benzene for 4 hours [229]. However, in the case of aluminium thiomethoxide, extended reaction times were required before any useable quantites of **335** were produced, albeit in poor yield. In both attempts, the thiol ester[280a] **336** predominated, the alkythio reagent behaving, at elevated temperatures, in an analogous fashion to the arylthio reagent at 5°C over the same period of time[273]. The formation of **335** was not optimized, as there exists a method for its synthesis that requires conventional, though lengthy, techniques [279a], and alternatively, one can envisage thionation [280b] of **336**

leading to the dithiopropanoate from which Beslin et al.[271] recently reported a quantitative transformation to **335**.

Deprotonation of **335** in THF at -78°C was followed by alkylation with halide reagents in a procedure that paralleled the reactions of **322** (Table 6).

TABLE 6

Reaction of the lithium ketene thioacetalide derived from 1,1,3-tris(methylthio)-1-propene(**335**).



335 337 338

Entry	Electrophile[g]	Ratio[a] 337(α):338(γ)		Yield(%)[b] 337+338
a	$(CH_3)_3SiCl$	80	20	35
b	$PhCH_2Br$	70	30	46
c	CH_3I[f]	67	33	--[c]
		(49	17)[d]	
		(85	15)[e]	

a Determined by ^1H NMR analysis.

b Isolated yields after chromatography on silica gel.

c Products detected (60 MHz ^1H NMR) but spectroscopic purity could not be achieved.

d See ref. 279 a).

e See ref. 271.

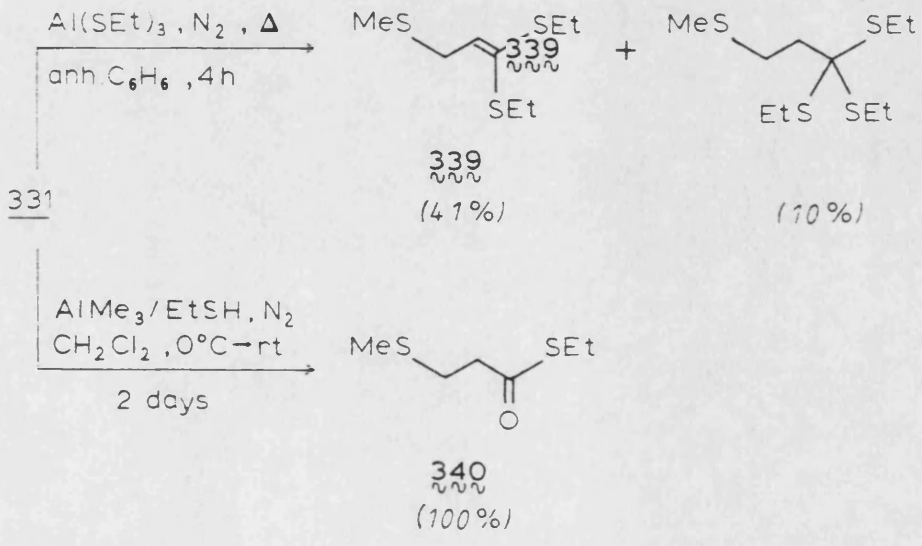
f It is known that iodomethane reacts at the α-site: see ref. 221a).

g For E in **337/338**, see Table 1.

Under these conditions α-alkylation of **335** is also uniformly favoured. However, the appearance of γ-alkylation in the acyclic structure (cf. Tables 5 and 6, entries a and b) gives some measure of the γ-regioselectivity induced by the comparatively sterically demanding methyl groups.

Unfortunately carbonyl compounds were excluded from this study. Hevesi et al.[279a] reported that under similar conditions, no significant regioselectivity was observed for **335**, but in the presence of HMPA the regioselectivity of hydroxybenzylation was convincingly γ-oriented and only 6% of the α-isomer was isolated.

The synthesis of 1,1-bis (ethylthio)-3-(methylthio)-1-propene (**339**) was accomplished from **331** in a procedure that for ethanethiol resulted in no contamination from the corresponding thiol ester **340** (Scheme 124). This



Scheme 124

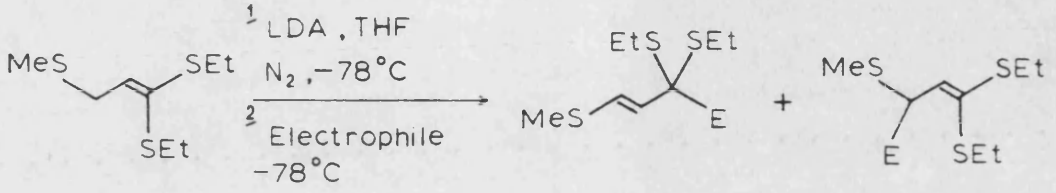
observation casts some doubt on the complete replacement of methyl groups by methylthio substituents in the aluminium reagent used to prepare **335**, although methanethiol was slowly introduced to $AlMe_3$ at ambient temperature for 30-60 minutes.

When the reaction conditions that Corey *et al.*[220b] employed to make **322** were applied to the synthesis of **339**, the thiol ester **340** was obtained in quantitative yield; isolated, unlike **322**, from a transparent, colourless dichloromethane solution. Obviously, use of the bis (dimethylaluminium) reagent enables an intramolecular step to follow the initial attack upon **331**, and allows the desired reaction to proceed at lower temperatures. When reaction is intermolecular, reduced temperatures result in transesterification only, an observation noted by Cohen *et al.*[273] for aluminium thiophenoxide. However, two observations bring the formation of aluminium thioethoxide itself into question. During the preparation of the alkythio reagent, an absence of white suspension was noted, and the addition of **331** did not ultimately cause the reaction mixture to become coloured. On hydrolysis of the aluminium salts, a relatively vigorous reaction ensued, forming the second point of difference with previous preparations.

The alkylation of **339** was seen to result in complete reversal of regiochemistry, favouring a higher proportion of γ-alkylation than that obtained with 1,1-bis(ethylthio)-1-propene[221d] (Table 7).

TABLE 7

Reaction of Metallated Ketene Dithioacetal **339** with Various Electrophiles.



339 341 342

Entry	Electrophile[e]	Ratio 341(α):342(γ)		Yield(%)[a] 341+342
a	MeSSMe	20	80[b]	75
b	CH_3I	34	66[c]	66
c	$PhCH_2Br$	27	73[b]	--[d]
d	cyclohexanone	30	70[b]	--[d]

a Isolated yields after chromatography on silica gel.

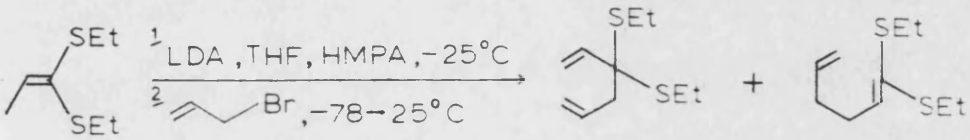
b Determined by ^1H NMR analysis.

c Determined from isolated yields.

d Products detected (60MHz ^1H NMR) but spectroscopic purity could not be achieved.

e For E in **341/342** see Table 1.

Although one would expect the steric effect of two geminal ethylthio groups to direct alkylation to the γ-site to a certain extent[221d] (Scheme 125), the inclusion of a mild anion-stabilising group at the γ-position reinforces the γ-regioselectivity to the extent that it becomes the dominant expression of reactivity for **339**. Both ketones and alkyl halides are seen, in the absence of HMPA, to react in the same manner.



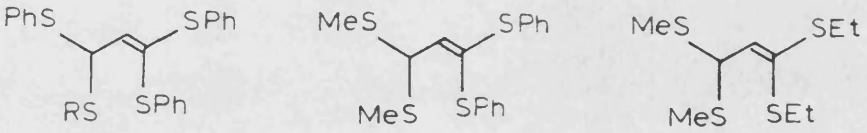
α 70 γ 30

Scheme 125. Ziegler *et al.*[221d] did not unfortunately report the α/γ ratio in the absence of HMPA.

In addition, the base-induced coupling of benzyl bromide was not noticed in the benzylation of **339**, although the analogous reaction with 1,1,3-tris(methylthio)propene (**335**) produced 1-bromo-1,2-diphenylethane in 76% yield.

2.4 Metallation of 1,1,3,3 -Tetrakissulphur-substituted propene systems. The search for a β-Hydroxy-β-lithioacrylate equivalent.

The formation of sulphenylated adducts in our investigation of ketene dithioacetalide regiochemistry provided a series of compounds for analogous deprotonation studies (Scheme 126).

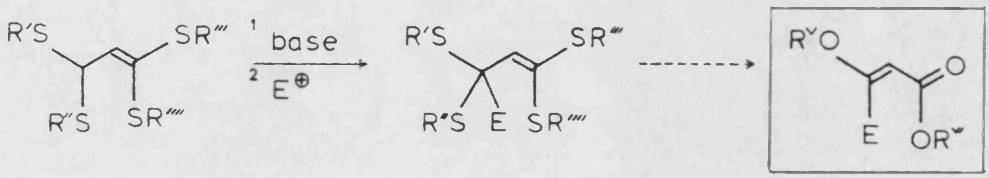


307r R=Ph 329e 342a

307q R=Me

Scheme 126

The aim at the outset of this study was to develop a tetrakissulphur-substituted propene that could be regarded as a β-hydroxy-β-lithioacrylate equivalent (Scheme 127), such β-functionally substituted acrylates yielding versatile building blocks **343** for tetronates, and other derivatives, which constitute many natural products [10a,c,111e,258].



343

Scheme 127

Our interest in these adducts was based upon our anticipation that the enhanced proton acidity arising from the presence of an additional thioether group[281] might

generate an additionally stabilised allylic carbanion despite the failure of **307a** to accommodate a second methyl residue. In addition, alkylation products would incorporate bissulphur-substituted carbon atoms that could be selectively deprotected, the S,S-ketal being resistant to the acidic conditions required for sulphur-separated ketene dithioacetal hydrolysis[282].

We found no evidence by NMR for formation of alkylation products with the tetrakisphenylthio propene **307r**, and attributed this observation to the enhanced steric hindrance [283] which must prevent effective approach of base reagents (Table 8). Steric repulsion between the phenylthio groups themselves would rule out any assistance from the C=C in weakening the allylic C-H bond because restricted rotation about the C-C bond would place the S-C-S groups in orthogonal planes. In the absence of base reactivity, the relatively nucleophilic alkyllithium reagents cleave the allylic C-S bond,reductively lithiating **307r**, this reaction being more pronounced with methyllithium (entry c). Alkylation of the resulting carbanion led to the formation of **307a**. This mode of reactivity is usually associated with selenium compounds[284], although it has been observed for sulphur compounds under special conditions[285].

TABLE 8

Attempted Reaction of **307r** with base/iodomethane[a].

Entry	Base[b]	Temperature (°C) 1. For anion generation; 2. After MeI addition.	Time(min) 1. for anion formn.	Products
a	LDA	-78 → -40 -78 → rt	ca.60	recovered **307r**
b	n-BuLi	0 0 → rt	15	recovered **307r**[d]
c	MeLi[c]	0 0 → rt	20	**307a**[e]
d	n-BuLi	0 0 → rt	60	recovered **307r**[d]
e	n-BuLi/ HMPA	0 0 → rt	60	recovered **307r**[d]

[a] All reactions conducted in THF solvent.

[b] 1.1 equivalents employed.

[c] 2.0 equivalents employed.

[d] Trace amounts of **305** detected.

[e] Possibly accompanied by trace amount dimethylated compound.

Stepwise methylsuphenylation of **326** provided **329e**, but even a reduction in the size of both of the heteroatom substituents at the γ-carbon atom was not sufficient to

allow metallation with LDA at -78°C. We turned our attention instead to the tetrakis(alkylthio)propene **342a**.

The formation of **342a** from the trissulphur compound **339** was accompanied by the minor α-adduct **341a** which could not be separated. The presence of **341a**, however, offered an NMR handle by which any reduction in the amount of **342a** could be easily detected. The alkylation of **342a** was largely unsuccessful (Table 9), the regular recovery of unreacted material punctuated with reductive lithiation in the case of alkyllithium reagent usage. On two occasions, use of LDA in the presence of HMPA resulted in an increase of the α/γ ratio (entries h and k), and the appearance of a singlet at δ 6.30 suggested that alkylation of **342a** had been partially successful (Figure 1). Unfortunately, this result was not reproducible, and there were several inconsistent observations (entry h vs. entry i) which suggested that **342a** was a compound on which we could not rely.

It has been previously demonstrated[283] that the tetrakis(alkylthio)propenes incorporating wholly methyl or ethyl substituents do not contain "active" hydrogen. Deprotonation studies were limited to a few examples, and a range of reaction conditions was not examined[286]. Although not put forward as a direct explanation, molecular models had revealed that steric hindrance between the alkylthio groups might lead to restricted rotation of the C-C bond. The reason why **342a** fails to react is therefore not very different from that concerning **307r**. We believed that reaction could be achieved with the analogous

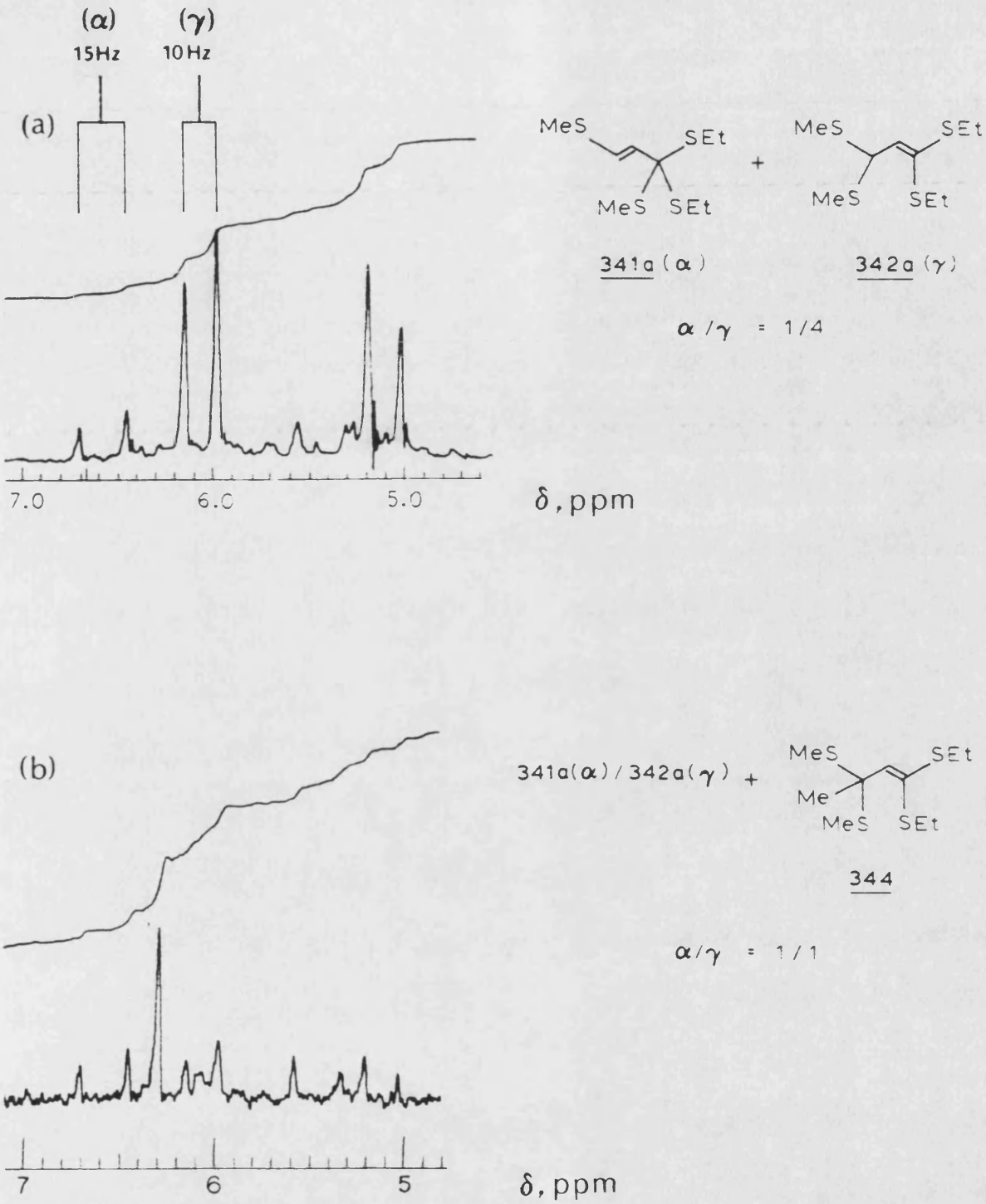


Figure 1. 60 MHz ^{1}H NMR Part spectrum (vinyl region) of **341a/342a** starting material (a), and result of reaction with LDA/HMPA/MeI (Table 9, entry h) (b).

TABLE 9

Attempted Alkylation of 1,1-Bis(ethylthio)-3,3-bis (methylthio)-1-propene (342a)

Entry	Base[a]	Conditions[b]	Electrophile	Products
a	LDA	THF,-78→-40°C ca.2.5hr	MeI,-78→rt 1.5hr	recovered **342a**
b	LDA	THF,-78→0°C (1 hr)	MeI,0°C→rt	recovered **342a**
c	LDA	DME,-78→-20°C (1 hr)	MeI,-78°C→rt	recovered **342a**
d	$(TMS)_2NLi$	THF,-78°C (30 min)	MeI,-78°C	recovered **342a**
e	$(TMS)_2NLi$	THF,-78→-40°C (1 hr)	MeI,-78°C	recovered **342a**
f	$(TMS)_2NK$	THF,-78 → 0°C (30 min)	D_2O,0°C	recovered **342a**
g	LDA/HMPA	THF,-78→-40°C (30 min)	D_2O,-78°C	recovered **342a**
h	LDA/HMPA	THF,-78→-20°C (1 hr)	MeI	**FP344** and **342a** (3:1)
i	LDA/HMPA	THF,-78→0°C (1 hr)	MeI,0°→rt	recovered **342a**
j	LDA/HMPA	THF,0°C(1.5 hr)	MeI,0°C	recovered **342a**
k	LDA/HMPA	DME,-78→-20°C (1 hr)	MeI,-78°C	**FP344** and **342a** (1:3)
l	LDA/HMPA	THF,-78→-20°C (1 hr)	PhCHO, -78→rt	recovered **342a**
m	n-BuLi	THF,0°C(30 min)	MeI,0°C	**339** and **342a** (1.6:1)
n	n-BuLi	THF,-78°C (30 min)	MeI,-78°C	**342b** and **342a** (ca.1:1)

cont..../

TABLE 9

Attempted ALkylation of 1,1-Bis(ethylthio)-3,3-bis (methylthio)-1 propene (342a)

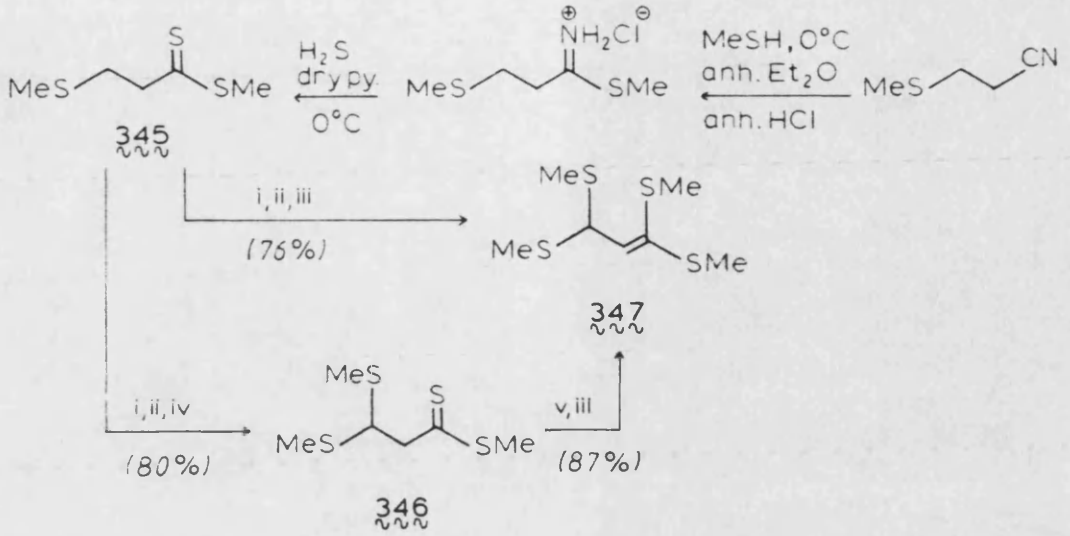
Entry	Base[a]	Conditions[b]	Electrophile	Products
o	t-BuLi	THF,-78→0°C (30 min)	D_2O,0°C	recovered **342a**
p	t-BuLi/ HMPA	THF,-78°C(2 hr)	PhCHO, -78°C	**339** and **342a** (1.3:1)

a 1.1 equivalents base employed; 3 equivalents of HMPA.

b Time in parentheses denotes duration at latter temperature (if applicable) before addition of electrophile .

tetrakis(methylthio)propene **347**, this compound being the least sterically congested system. Even if the methylthio substituents could not achieve coplanarity to afford the required resonance - stabilised allylic carbanion, we would be dealing with a thioacetal proton very similar electronically to the acidic C-2 protons of 1,3-dithiane for which the alkyllithium reagents were adequate bases.

We required a procedure for the synthesis of **347** that did not involve alkylation of the trissulphur-substituted ketene dithioacetal **335**, as it is known [22la,279] that electrophiles would react at the α-site [287]. For this purpose, we chose to use the dithioester **345** reported by Beslin et al. [271] and prepared from the corresponding nitrile[288] by a Pinner reaction[289] (Scheme 128).



Scheme 128 . (i) *n*-BuLi, THF, −78°C; *s*-BuLi, −50°C, 1h; (ii) MeSSMe, −78°C, 30min; (iii) MeI, −78°C; (iv) NH_4Cl(aq); (v) LDA, THF, −78°C, 30min.

Initial thioenolate anion formation from **345** could be achieved with n-BuLi, in a slight departure from the literature procedure (in which MeLi was used). However, s-BuLi was necessary for subsequent allylic deprotonation. Use of either n-BuLi or t-BuLi as the second base resulted in formation of **335** only, this being a contaminant in the direct procedure involving s-BuLi. A stepwise approach to **347** via **346**, enabled purification of the intermediate to be effected prior to reaction with LDA[290], use of which resulted in a clean conversion to **347**[236].

Unfortunately, **347** was also resistant to alkylation under a range of conditions (Table 10).

TABLE 10

Attempted Alkylation of 1,1,3,3-Tetrakis(methylthio)-1-propene (347).

Entry	Base[a]	Conditions[b]	Electrophile[b]	Products
a	LDA/HMPA	THF,-78→-20°C (30 min)	MeI,-78→-20°C	**347** and F.P.[c] (2.5:1)
b	LDA/HMPA	THF,-78→-20°C (1 hr)	PhCHO,-78→rt	recovered **347**
c	LDA	THF,-78→-20°C (1 hr)	PhCHO,-78→rt (15 hr)	recovered **347**
d	LDA	Et_2O,-78→-20°C (1 hr)	D_2O,-20°→rt (1 hr)	recovered **347**
e	s-BuLi	THF,-78→-30°C (30 min)	PhCHO,-78→0°C	recovered **347**
f	s-BuLi/ TMEDA	THF,-78→-20°C (1 hr)	PhCHO,-78→rt (15 hr)	recovered **347**
g	s-BuLi	THF,-78→0°C	D_2O,0°C	recovered **347**
h	t-BuLi	THF,-78→0°C (1 hr)	D_2O,0°C	**347** and reductive lithiation
i	n-BuLi	Et_2O,-78→-50°C (30 min)	D_2O,-50→rt (30 min)	recovered **347**
j	n-BuLi	Et_2O, 0°C (1 hr)	D_2O,0°C	**347** and reductive lithiation
k	n-BuLi	Et_2O,-30→0°C ca. 1 hr	D_2O,0°C	**347** and reductive lithiation

a 1.1 equivalents base employed; 3 eq. HMPA/TMEDA.

b Time in parentheses denotes duration at latter temperature (if applicable).

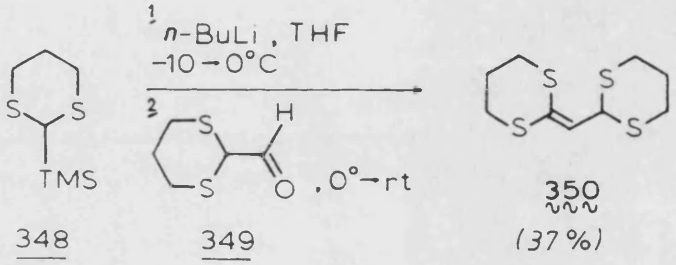
c Assignment based on observation of singlet at δ 5.98 (^{1}H NMR) (cf. Figure 1) downfield of AB quartet of **347**.

It was hoped that the problems involved with **347** could be circumvented by using the 3,3-bis(methylthio)dithioester **346**. Unfortunately, subjecting **346** to the double deprotonation conditions attempted for the β-alkylation of **345** led to multicomponent reaction mixtures in all reactions examined.

Circumstantial evidence indicates however that the desired adducts are formed on treatment of **347** with LDA at $0^{o}C$ and allowing the yellow solution to stir at ambient temperature for ca. 1 hour. This manifested itself as a positive response to $PdCl_2$ development upon t.l.c. analysis [291] after quenching the dark orange/red mixture with the electrophilic reagent. Although the reactions were reproducible, the resulting adducts were unstable, and even immediate chromatographic purification was attended by reversion to starting materials.

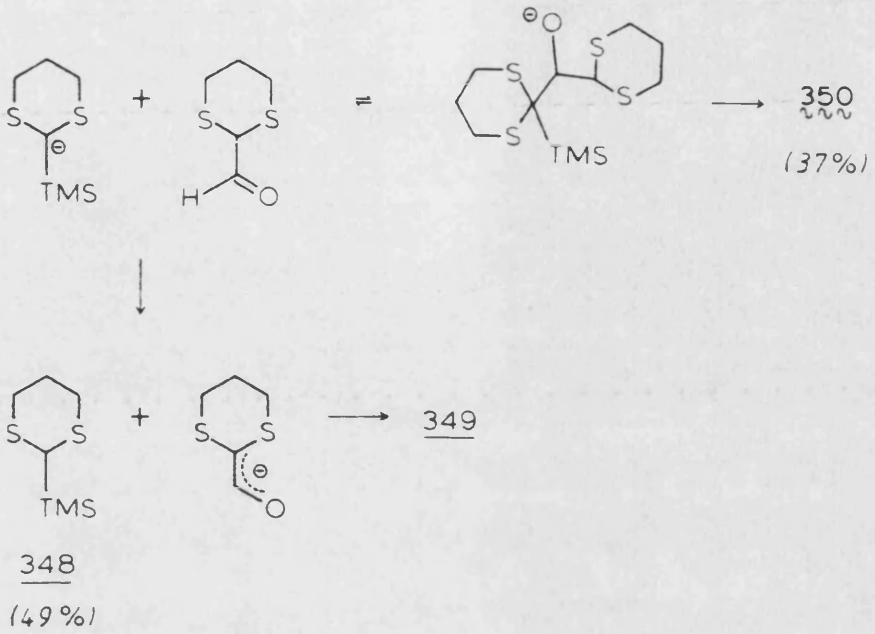
In seeking a reagent that would afford stable, isolable products upon alkylation, we decided to lock the heteroatom substituents in the conformationally restricted cyclic structure **350**. It is apparent from earlier work[221d] that dithiane-based ketene dithioacetals (alkylidene dithianes) offer a less sterically hindered environment than the acyclic analogues with respect to the approach of electrophiles. Perhaps this observation would also be applicable to the bisdithiane compound **350**, allowing free rotation of the C-C bond and the successful accommodation of substituents.

The Peterson olefination[292a] was chosen for direct access to **350**.[292b] The main criteria were the convenience of the reaction and the ready availability of the starting materials in quantitative yields. 2-Trimethylsilyl-1,3-dithiane[293] (**348**) was metallated with n-BuLi at -10°C and treated with 2-formyl-1,3-dithiane[294] (**349**) at 0°C (Scheme 129). Warming the mixture to ambient temperature afforded **350**, but in poor yield, irrespective of the choice of solvent (THF or DME). The Peterson olefination is tolerant of almost all substitution patterns of the carbonyl derivative employed: only highly-hindered ketones give lower than 70% yields[292a]. This access to **350**, however, differs



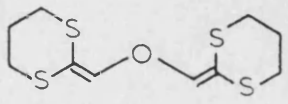
Scheme 129

from the foregoing methods in that the carbon skeleton is formed conjunctively. Consequently, use of the extremely enolisable aldehyde **349** is thought to give poor yields of **350**, possibly via establishment of equilibrium, followed by prototropy, so that both the product and starting materials are present in the reaction mixture (Scheme 130).

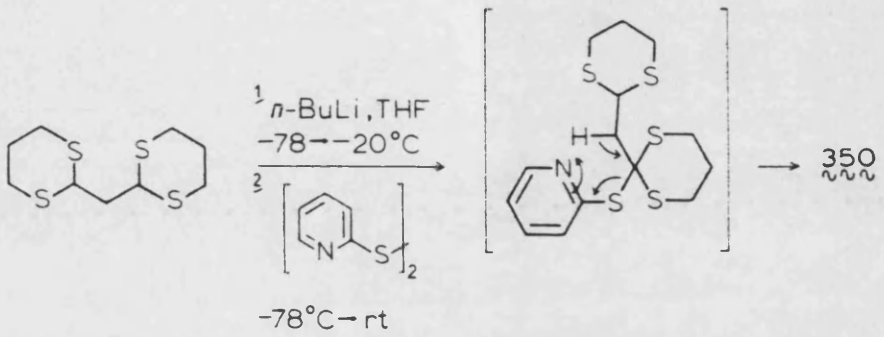


Scheme 130

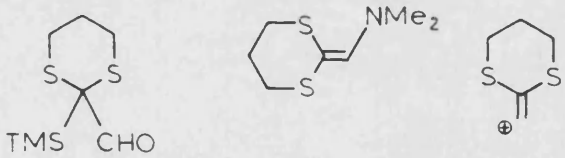
Fortunately radial chromatography could separate **350** from **349**, to afford the ketene dithioacetal as an oil. At this stage we did not attempt to optimise the reaction conditions, although to date a procedure[269b] has been employed that affords **350** as a crystalline solid (75%): mp 77-79°C (from methanol)[295a] (Scheme 131). This procedure also avoids the formation of byproduct **351** (17%) whose presence was evident upon chromatography every time **350** was isolated from the mono-dithiane starting materials.



351



Scheme 131 . The saturated analogue of **350** is itself a crystalline solid , prepared according to ref. *295b* .



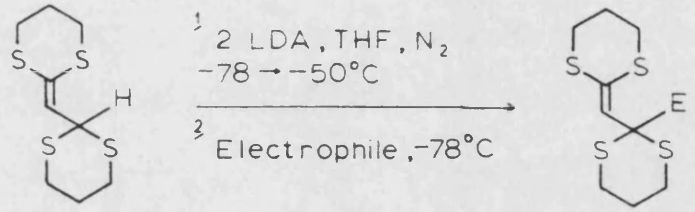
352 353 354

Conceptually the disubstituted 1,3-dithiane **352** would have proved an ideal starting material. However, its preparation from **348** and DMF is known[296a] to afford dimethylamino methylene -1,3-dithiane (**353**)[296b], whereas the alternative procedure from **349** would lead to O-silylation. The compound **352** would have a wider role as the cation equivalent **354** useful for a generalised ketene dithioacetal synthesis.

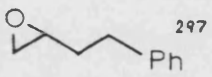
Metallation of **350** with two equivalents of LDA and reaction with electrophiles successfully formed the adducts **355a-e** (Table 11), adduct **355d** providing a structurally uncomplicated model for subsequent cyclization studies.

TABLE 11

Reaction of the metallated bisdithiane ketene dithioacetal **350** with various electrophiles.



350 355

Entry	Electrophile	E in 355	Yield (%)[a]
a	CH_3I	CH_3	98[b]
b	PhCHO	CH(OH)Ph	76[b]
c	$C_5H_{11}CHO$	$CH(OH)C_5H_{11}$	76[c]
d		CH_2CH_2OH	61[c]
e		$CH_2CH(OH)(CH_2)_2Ph$	78[c]

a Isolated yields after chromatography on silica gel.

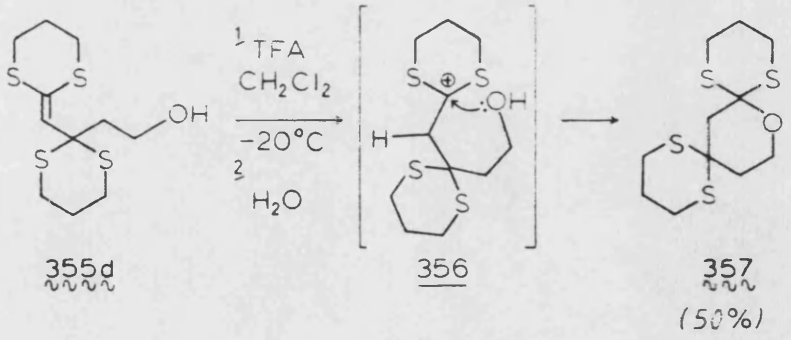
b Using **350** prepared according to Scheme 131.

c Using **350** prepared according to Scheme 129.

The recognition that sulphur does not only stabilise a negative, but also a positive charge on the neighbouring carbon atom[298], means that ketene dithioacetals are well suited as internal traps for carbocationic cyclizations [299].

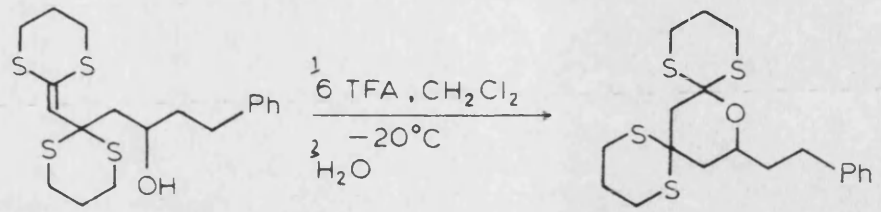
Unlike the so-called 'sulphur separated[229] ketene dithioacetals, alkylidene dithianes are not hydrolysed to acyl sulphides under acidic conditions[201,292b]. Instead bicyclic dithio-orthoesters are formed[256c] when internal hydroxyl groups are present, and this suited our purposes.

A hetero-cyclization was initiated using TFA by formation of a bissulphur-stabilised carbocation (dithienium ion) **356** which was intramolecularly intercepted by the nucleophilic hydroxyl oxygen[256c] to afford the dithiaoxaspiro system **357**, a doubly protected tricyclic butenolide ring system[221a,299b] (Scheme 132). Reaction of the adduct **355e** with ca. 6 equivalents of TFA at reduced temperature also afforded a crystalline tricyclic compound **358** (Scheme 133).



355d 356 357 (50%)

Scheme 132. See ref. *295b* for the corresponding cyclohexane-1,3-dione based adduct, which is a solid.



355e

358

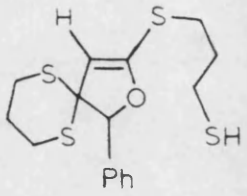
(85%)

358

Scheme 133

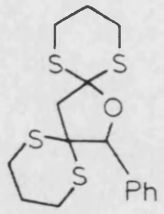
The formation of the tetrahydrofuran series was not so straightforward. Treatment of **355b** and **c** with ca. 6 equivalents of TFA resulted initially in the appearance of single components at higher t.l.c. Rf values. Within 1 min, however, the initially-formed components were seen by t.l.c. to have subsequently reacted further to afford compounds that were only slightly less polar than the starting alcohols. The unifying features in these reactions were the presence of a vinyl singlet at δ 5.9-6.1 in the NMR, and an unmistakable thiol odour not evident in the cyclizations of **355d** and **e**.

Unlike the spectrum from **355c**, which was complicated by the methylene resonances of the pentane side chain, ^{1}H NMR analysis of the product arising from **355b** clearly revealed the propanethiol side chain, indicating that cleavage of one of the dithiane rings had followed cyclization. The weak S-H stretch was also visible at 2570 cm^{-1} in the infra-red 300.



359

On the basis of our observations concerning the mild hydrolysis of the tetrahydropyran series, we suspected that the dithio-ortho ester functionality had been hydrolysed in the presence of excess acid. This is supported by Otera et al.[301] who noticed that a phenylthio group α to the methoxy group is readily cleaved under mild acidic conditions. When the amount of TFA was drastically reduced, the 2,3,5 - trisubstituted tetrahydrofuran derivative **360** was produced cleanly in 63% yield. Use of acetic acid to initiate cyclization also prevented formation of **359**, but formation of **360** was, accordingly, a very slow process; as our experience with acetic acid has shown[302] (cf. formation of **99**).



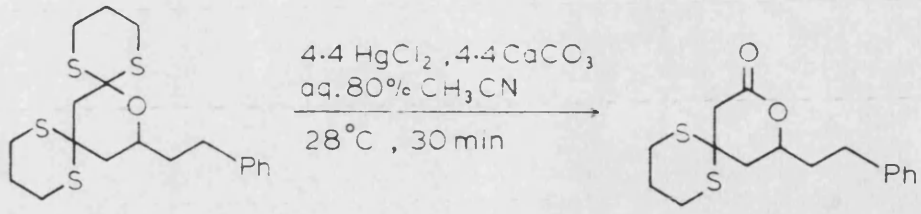
360

The successful construction of the tricyclic adducts **358** and **360** provides a route to a wide variety of dihydropyrone[10c] and tetronate[10a,303] derivatives

respectively, providing that the appropriate electrophilic substrates are available. The synthesis , from **358**, of one of the plant constituents of Piper methysticum Forster (Kawă)[304], possessing a 5,6-dihydro-4-methoxy-2H-pyran-2-one skeleton[10c,304,305], is exemplary; and established an operational equivalency between the lithium ketene dithioacetalide derived from **350** and the β-alkoxy-β-lithioacrylate anion[111e].

Deprotection of **358** was best achieved in a stepwise manner; use of mercuric chloride being compatible with the desire to differentially hydrolyse the dithiane-substituted centres. The conditions required for the mercury(II)-promoted hydrolysis of 1,3-dithianes may be correlated with the electron-supplying ability of the substituents at C-2. Although the hydrolysis by the mercury method of 2,2-dialkyl derivatives is generally very facile, reflux temperatures over a period of 4-6 hours are still required to generate the carbonyl group[306]. On the other hand, the same procedure brings about dithio-ortho ester cleavage at ambient temperature[302]. In this way, **358** was smoothly converted to **361** in 30 minutes[307] (Scheme 134).

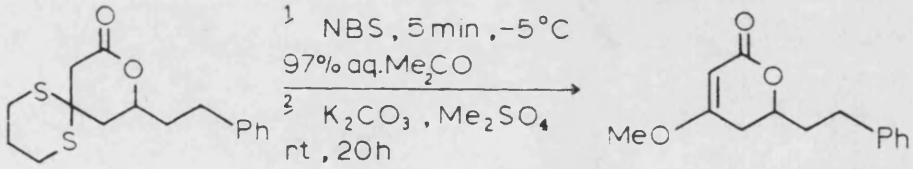
To complete the synthesis, we chose to oxidatively hydrolyse **361** using a N-halosuccinimide reagent[306], this procedure being noted for affording the corresponding carbonyl compound rapidly at low temperatures. The product of this reaction was immediately subjected to methylation conditions using dimethyl sulphate [304c,305a,308] in the



358 361 (69%)

Scheme 134

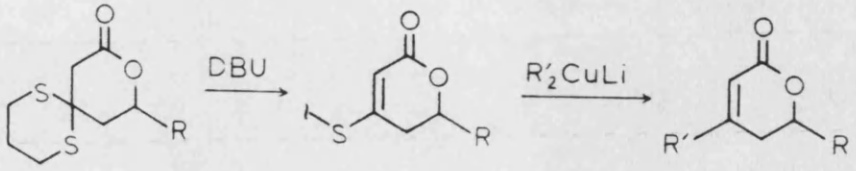
presence of potassium carbonate at ambient temperature to give (±)-dihydrokawain[309,310] (**362**) in 15% overall yield from **358** (Scheme 135).



361 362 (30%)

Scheme 135

In addition, interruption of the deprotection sequence to the mono-dithiane derivative stage allows, in principle, the introduction of substituents other than alkoxy at C-4[263] (Scheme 136). Substitution at all carbon atoms of the 5,6-dihydropyran-2-one system has been thoroughly covered by Carlson *et al.*[10c].



Scheme 136

2.5 Conclusion

Lithiation of 1,1,3-tris(phenylthio)-1-propene (**305**) and reaction with a range of electrophiles was shown (Table 1) to give exclusively the γ -substituted product irrespective of the nature of the electrophile [218] (entry a vs. entry m), the relative hardness of the electrophile leaving group [221c] (entry a vs. entry b), the relative hardness of the electrophilic centre itself [221a] (entry m vs. entry n), and the inclusion of cation-coordinating cosolvents [221b] (entry f vs. entry g).

Reactions of ambident compounds are classically treated by assuming that product formation is dependent upon the interplay of "charge control" and "orbital control". Any deviations observed in the rules concerning electrophilic attack at heteroatom substituted allylic ambident anions are normally attributed to steric effects.[311] The regiochemistry of the allylic anion derived from **326** additionally supports the view that a 1,1-bis(phenylthio) substitution pattern at a trigonally-hybridised carbon atom totally restricts access to incoming electrophiles; precluding bond formation at that site. The screening of

the α-site is depicted in Figure 2. It has been demonstrated that for γ-regioselectivity, the γ-phenylthio group itself is not essential, although its presence in a similar system (Scheme 117) is believed to exert noticeable electronic effects.[271] In our use of **305**, the presence of the γ-phenylthio functionality as an expression of latent unsaturation, enables **305** to act as a β-lithioacrylate

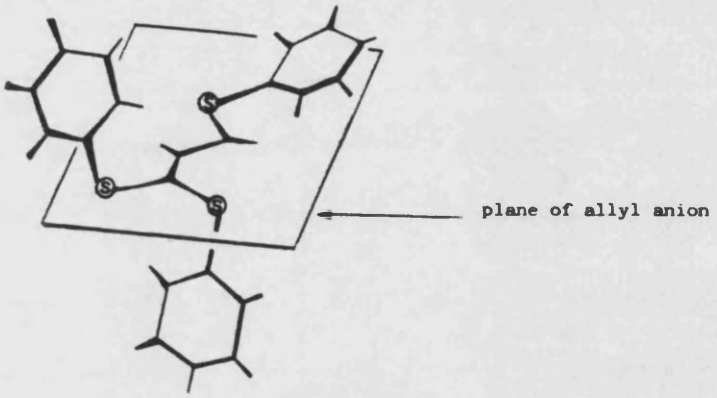


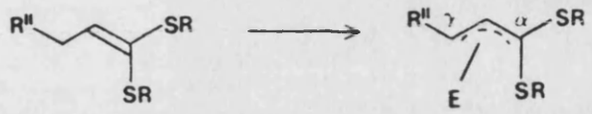
Figure 2. Steric hindrance at C-1 of the lithium ketene dithioacetalide **306**.

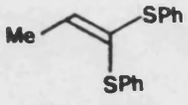
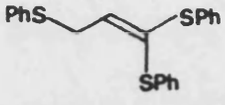
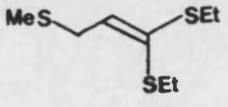
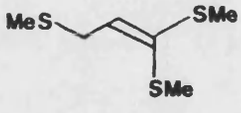
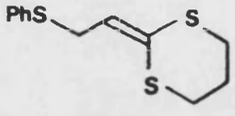
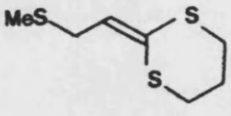
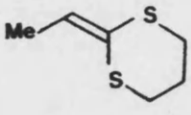
equivalent. Use of **326** in a similar way would provide a β-lithiopropionate equivalent.

The regiochemical preferences of the ketene dithioacetals described in this programme are summarised in Table 12. In those structures in which steric effects are not so pronounced, the underlying electronic effects can be perceived. The distribution of alkylation products between the two reactive centres then depends on how balanced the steric and electronic influences are, although under no circumstances was there a regioselective distinction between ketones and alkyl halides. In light of the results obtained

TABLE 12

Product Distribution in the Alkylation of Ketene Dithioacetals



		γ : α	
(a)		100 : 0	
(b)		100 : 0	
(c)		80-70 : 20-30	
(d)		40-30 : 60-70	(Ref. 271, 279a)
(e)		40-30 : 60-70	
(f)		0 : 100 (20 : 80 with cyclohexanone)	(Ref. 220b)
(g)		0 : 100	(Ref. 221d)

by Hevesi et al.[279a] concerning alkylation of **335** with benzaldehyde/HMPA, the omission of carbonyl compounds (Table 6) is unfortunate.

In entries (e) and (f) (Table 12), α-alkylation is favoured because the 1,3-dithiane ring is sterically undemanding. In this case, however, inclusion of a γ-phenylthio group (entry e) stabilises the γ-anionic site to a greater extent than does a γ-methylthio group, as evidenced by the relatively greater incidence of electrophilic attack at that position. The difference between phenyl and methyl heteroatom substituents has been noted previously in selenium stabilised allylic anion regiochemistry.[279a] Whereas 1,3-bis(phenylseleno)propene (**194**) can be deprotonated easily by LDA in THF, this base is not strong enough to deprotonate 1,3-bis (methylseleno)propene due to the lower acidity of the allylic hydrogens in the latter compound (see also Table 4).

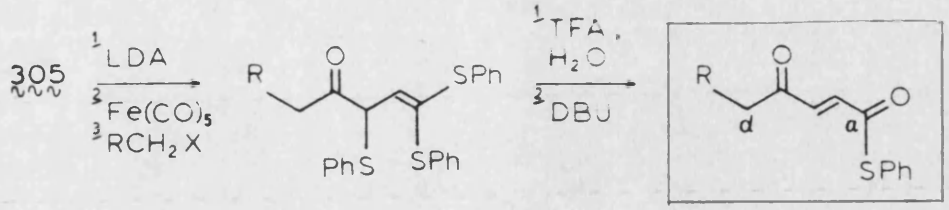
The behaviour of **305**, therefore, can perhaps be reviewed as arising from a 'push-pull' situation: the γ-phenylthio group electronically favours electrophilic attack at the γ-position, and, acting in concert, the α-phenylthio groups sterically direct electrophiles to reaction there. However, the degree to which the two influences contribute to the observed γ-regioselectivity cannot be ascertained as the former is masked by the latter. A more interesting examination would result from the alkylation of 1,1-

bis(ethylthio)-3-(phenylthio)-1-propene, combining those elements from both entries (c) and (e) which are believed to enhance the γ-regioselectivity in compounds **339** and **323** respectively.

In those compounds containing only a relatively mild γ-anion-stabilising group (entries c and d), a greater degree of γ-alkylation is noted for an increase in the steric bulk of the heteroatom susbstituents at C-1;[221d] although the dramatic inversion of regioselectivity observed in progressing from 1,1-bis (ethylthio)propene (Scheme 125) to **339** was not anticipated.

2.6. Recommendations for Further Work

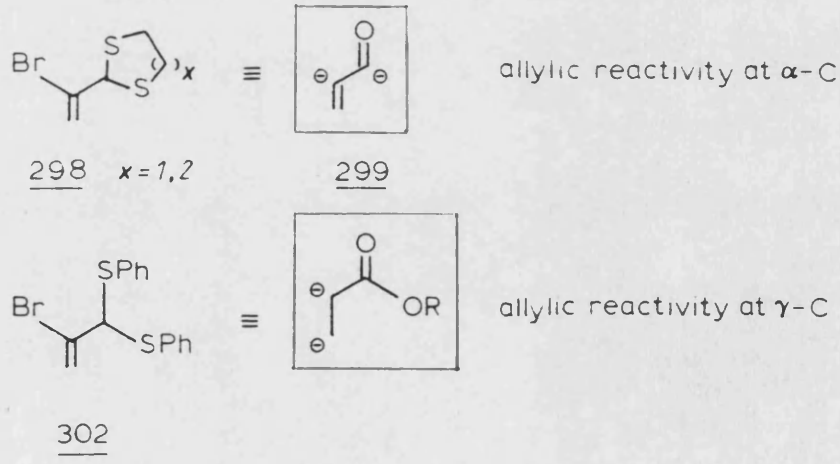
1. Although the alkylation of **305** has been extensively studied,[237] a similar high yielding acylation procedure remains to be found, in spite of some initial successes[239] (Table 1, entries u and v). A method exists for the acylation of 2-alkyl-1,3-dithiolanes using iron pentacarbonyl,[312] which was briefly examined for its applicability to **305**.[239] A more thorough investigation into the optimum reaction conditions required could lead to a series of γ-oxo-α,β-unsaturated thiol esters; useful synthetic equivalents for macrolide synthesis for which Ley *et al*.[258] have noted a conspicuous absence to date (Scheme 137).



Scheme 137

2. Incorporation of some feature of chirality at the γ-position of **305**, either by use of a chiral sulphoxide, or an S-appended chiral auxiliary could be employed to induce chirality at C-3 upon alkylation.

3. Homoenolate dianion equivalents in which the reactive centres have a 1,3- relationship are now fairly well established.[149a,b,225]. It would be interesting to return to our original objective, the synthesis of **298**(x=1,2), as C-2 functionalisation remains an attractive option.



Scheme 138

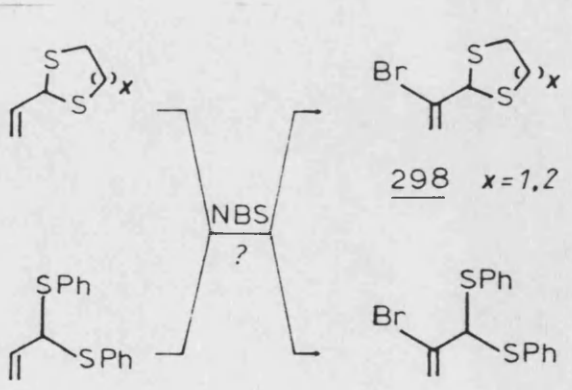
Our observation of the steric effects of phenyl heteroatom substituents would enable us to devise two dianion equivalents. Compounds **298** and **302** (Scheme 138) could each be sequentially metallated, affording products of 1,2-dialkylation.

This strategy depends for its success, on the following:

1. The efficient syntheses of compounds **298** and **302**, bearing in mind our initial difficulties;

2. The stepwise generation of the anionic sites in a discriminatory manner.

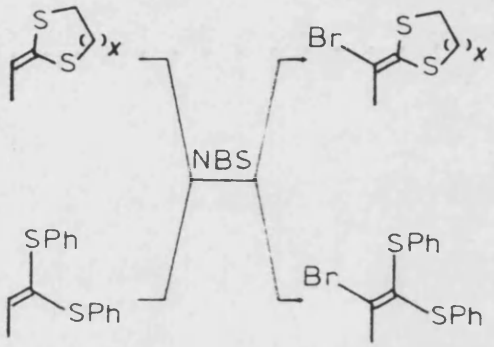
1. We have shown that as precursors to lithium ketene dithioacetalides (**290**), ketene dithioacetals and vinyl S,S-acetals are equally suited (see Scheme 106), an observation previously recorded by Murphy et al.[221c] The solution to this problem then reduces to which of the two classes of ketene dithioacetalide precursor can be brominated at C-2 (Schemes 139 and 140).



298 x=1,2

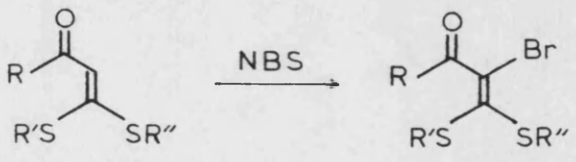
302

Scheme 139



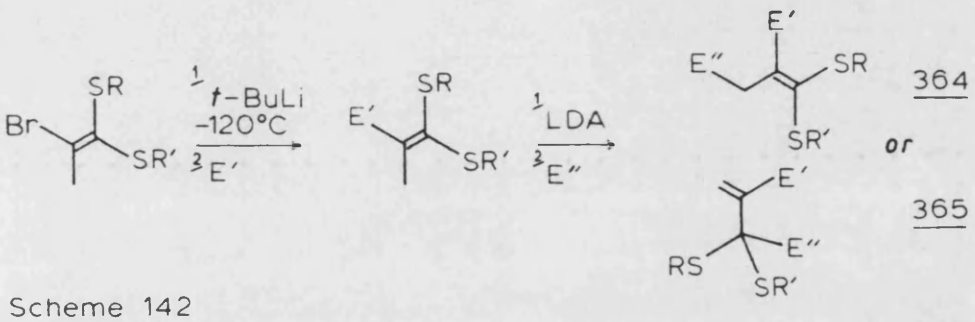
Scheme 140

A procedure for brominating ketene dithioacetals using NBS is known [313] (Scheme 141), and as NBS is also used to oxidatively hydrolyse 2-substituted-1,3-dithiane derivatives[306], ketene dithioacetals offer several advantages over the vinyl S,S-acetal counterparts.



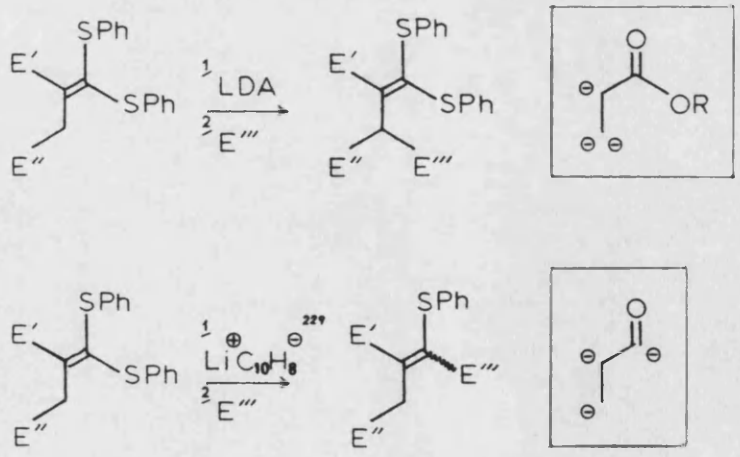
Scheme 141

2. It has been shown[226] that at very much reduced temperatures, halogen-metal exchange can be effected without concomitant allylic deprotonation. Alkylation of the C-2 vinyl carbon atom would then have to be accomplished first (Scheme 142).



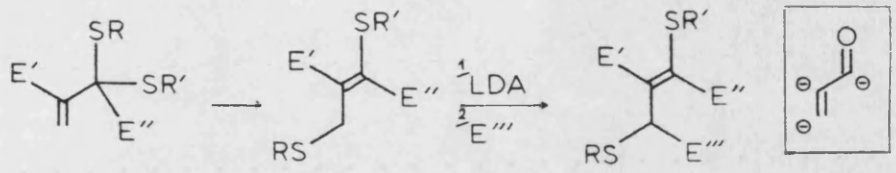
Scheme 142

Compound **364**(R,R'=Ph) could then be manipulated further providing that the electrophilic groups already present are not prone to further reaction or allylic deprotonation (Scheme 143).



Scheme 143

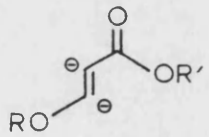
In those instances in which **365** contains groups which can be independently manipulated (e.g. R=R'=SMe), it might be possible to functionalise all the skeletal carbon atoms after an initial allylic thioether rearrangement (Scheme 144),



Scheme 144

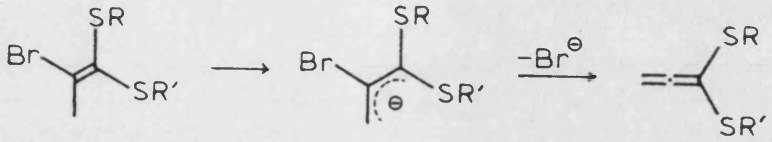
a process which has been previously achieved[301], but not via successive alkylation steps: E^1 is normally already present.

Similarly, the introduction of bromine in **350** would provide the β-alkoxy dianion equivalent **366.**

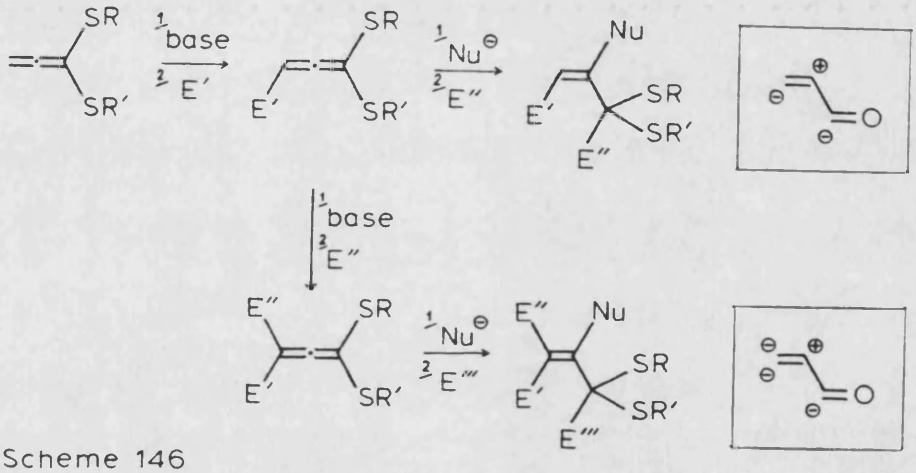


366

A problem that can be envisaged arises from a situation in which allylic deprotonation precedes halogen-metal exchange (e.g. with LDA), to form 1,1-bissulphur-substituted allenes (Scheme 145). In this event, the allene products themselves could be useful in constructing a synthon for a functionalised enone unit in which all the reactive sites arise by umpolung,[314] (Scheme 146).



Scheme 145



Scheme 146

EXPERIMENTAL

3. EXPERIMENTAL

Instrumentation and Experimental Techniques

Infrared (IR) spectra were recorded in the range 4000-600 cm^{-1} using Perkin-Elmer 197 and 1310 grating spectrophotometers, with 0.05 mm polystyrene film as a calibration reference (1601.4 cm^{-1} absorption) and peaks are reported in wavenumbers (cm^{-1}). Spectra of liquid samples were taken as thin films, or as solutions in $CHCl_3$. Spectra of solid samples were taken in $CHCl_3$ solution, unless otherwise stated.

Routine mass spectra from both electron ionisation (E.I.) and chemical ionisation (C.I., reagent gas isobutane), and high resolution accurate mass determinations were recorded with a VG Analytical 7070E instrument with a VG 2000 data system at an ionising potential of 70 eV. Where possible, the molecular ion peak ($M^{+\cdot}$) and base peak are indicated, as are all sizeable fragmentations with assignments.

Proton magnetic resonance (^1H NMR) spectra were recorded at 60 MHz on Hitachi Perkin-Elmer high resolution R-24B and Varian Anaspect EM-360 spectrometers, on JEOL 100 MHz, 270 MHz, and Bruker 400 MHz spectrometers, using the SERC facility at Warwick University. ^{13}C NMR spectra were determined with a JEOL FX90Q or GNM GX FT 270 spectrometer. ^1H and ^{13}C NMR spectra were recorded, unless otherwise noted, in $CDCl_3$, and are expressed in parts per million (δ) downfield from internal tetramethylsilane. Multiplicities are given as follows: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp), and are uncorrected. Elemental microanalyses were carried out using the Carlo Elba 1106 Elemental Analyser.

For experimental procedures of a general nature, a complete general description is given and subsequent details for actual examples include quantities of reagent, yield, and characterisation details.

Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide during reactions and for assessing the purity of compounds. Merck DC-alufolien Kieselgel 60 F_{254} sheets containing fluorescent indictor were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light, and developing with a 7% (w/v) methanol solution of *dodeca*-molybdophosphoric acid (PMA) followed by warming of the t.l.c. plate.

Preparative thin layer chromatography (PLC) was carried out using 20 x 20 cm glass plates coated with a 1 mm layer of silica gel 60 F_{254} s (Merck) with a concentrating zone 4 x 20 cm.

Unless otherwise stated, petroleum refers to petroleum spirit boiling point range 60-80 °C. This was distilled before use as eluant in column chromatography.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 and 60 H silica gel (Merck) for reaction component separations. A pressure gradient was developed using a small, commercially available hand bellows (Gallenkamp). In all cases, columns were prepared in petroleum, and chromatography was carried out with petroleum as the initial eluant, then eluting with ethyl acetate-petroleum mixtures of steadily increasing polarity. Material to be chromatographed was pre-adsorbed onto the column support and applied as a thin layer to the top of the column.

In those cases where reduced pressure distillation was difficult, if not destructive of the heavier compounds, or when column chromatography

was particularly difficult, very pure samples were obtained by employing preparative, centrifugally accelerated, thin-layer radial chromatography (Model 7924 Chromatotron). 2 mm absorbent layers (silica gel PF_{254} type 60 TLC from Merck) coated on circular glass plates were used for large sample loadings of up to 300 mg total sample.

Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenone ketyl under dry nitrogen until anhydrous. This was re-distilled immediately prior to use.

Glassware used for low temperature alkylation reactions was baked in an oven at 120 °C for *ca.* 12 h, and allowed to cool in a desiccator over $CaCl_2$. Flasks and stirring bars were, however, additionally flame dried under dry nitrogen.

In all experiments, the excess solvent was evaporated with a Büchi rotary evaporator by using water aspirator reduced pressure, at room temperature to avoid unnecessary heating. All yields quoted are of purified products, and are uncorrected unless otherwise stated.

All other general reagents and solvents were purified when required, and where necessary, dried using the methods described by Perrin *et al.*[315] and those in 'A Textbook of Practical Organic Chemistry' (A.I. Vogel, 4th edition, Longman, London, 1978).

2-Bromo-1,1,3-tris(phenylthio)propane (304)

Thiophenol (2.7 g, 2.51 ml, 24.5 mmol) was added dropwise to a stirred solution of α-bromoacrolein[232] (1.0 g, 7.41 mmol) in dry, distilled dichloromethane (24 ml) at ambient temperature. After 10 min, $BF_3.OEt_2$ (0.55 g, 0.48 ml, 3.9 mmol) was added dropwise at ambient temperature, producing an opaque, yellow mixture which was stirred for *ca.* 30 min. The mixture was then poured into 10% sodium hydroxide solution (50 ml). The organic layer was separated and washed exhaustively with 10% sodium hydroxide solution (5 x 50 ml) until no trace of thiophenol could be detected. The organic extract was washed with brine (50 ml), dried (Na_2SO_4), and concentrated under reduced pressure to afford the bromopropane (304), which was purified by flash column chromatography eluting with 10% ethyl acetate/petroleum, to give (304) (1.9 g, 58%): t.l.c. R_f 0.59 (10% ethyl acetate/petroleum); IR (thin film) 3060, 1580, 1470, 1435, 1020 cm^{-1}; ^1H NMR δ (100 MHz) 7.60-6.95 (15H, m, SPh), 4.98 [1H, d, J 1.5 Hz, $C\underline{H}(SPh)_2$], 4.24 (1H, m, CHBr), 3.93-3.35 (2H, m, CH_2SPh); ^{13}C NMR δ 133.54-127.31 (SPh), 63.87 ($\underline{C}HBrCH_2$), 55.42 [$\underline{C}H(SPh)_2$], 40.09 (CH_2); MS (E.I.) m/z (relative intensity) 448 (0.47, $M^{+\cdot}$ incorporating ^{81}Br), 446 (0.47, $M^{+\cdot}$ incorporating ^{79}Br), 366 (5.7, $M^{+\cdot}$-HBr), 338 (4.1, $M^{+\cdot}$-PhSH), 336 (4.5, $M^{+\cdot}$-PhSH), 257 (6.3), 147 (100); m/z calculated for $C_{21}H_{19}{}^{79}BrS_3$ 445.983, found 445.991; m/z calculated for $C_{21}H_{19}{}^{81}BrS_3$ 447.981, found 447.978.

1,1,3-Tris(phenylthio)-1-propene (305)

To a stirred solution of 2-bromo-1,1,3-tris(phenylthio)propane (304) (5.0 g, 11.2 mmol) in dry, distilled dichloromethane (50 ml) was added dropwise DBU (1.9 g, 1.84 ml, 12.3 mmol) at ambient temperature. The

resulting dark orange solution was stirred at ambient temperature for 1.5 h. The mixture was then poured into 0.5 M aqueous HCl (100 ml). The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated *in vacuo*.

Purification of the residue by flash column chromatography provided, on elution with petroleum, the ketene thioacetal (305) as a pale yellow oil (3.4 g, 83%): t.l.c. R_f 0.63 (10% ethyl acetate/petroleum); IR (thin film) 3050, 1575, 1465, 1430, 1210, 1065, 1020 cm^{-1}; ^1H NMR δ (60 MHz) 7.30-6.70 (15H, m, SPh), 6.06 (1H, t, J 7.5 Hz), 3.76 (2H, d, J 7.5 Hz); ^{13}C NMR δ 135.92 (β-CH), 134.73-126.61 (SPh), 34.51 ($CH\underline{C}H_2SPh$); MS (E.I.) m/z (relative intensity) 257 (100, $M^{+\cdot}$-SPh), m/z calculated for $C_{15}H_{13}S_2$ ($M^{+\cdot}$-SPh) 257.041, found 257.044.

Convenient 'one-pot' procedure for the preparation of *1,1,3-Tris(phenylthio)-1-propene* (305)

Thiophenol (9.96 g, 9.28 ml, 90.4 mmol) was added dropwise to a stirred solution of α-bromoacrolein[232] (4.0 g, 29.7 mmol) in distilled dichloromethane (70 ml) at ambient temperature. After 10 min, $BF_3.OEt_2$ (2.22 g, 1.92 ml, 15.6 mmol) was added dropwise, forming an opaque, yellow mixture. The mixture was stirred for *ca.* 30 min, and then poured into 10% sodium hydroxide solution (100 ml). The organic layer was separated, and washed with more 10% sodium hydroxide solution (5 x 100 ml). The organic extract was washed with brine (100 ml), dried (Na_2SO_4), and the drying agent removed by filtration.

To this orange solution was added DBU (4.6 g, 4.5 ml, 29.9 mmol) dropwise at ambient temperature with stirring. After *ca.* 30 min, (305) was isolated and purified, as described previously, to give a very pale yellow oil (8.9 g, 83%).

General procedure for the alkylation of *1,1,3-Tris(phenylthio)-1-propene* (305)

n-BuLi (0.69 ml, 1.1 mmol, 1.6 M in hexane solution) was added dropwise to a stirred solution of distilled di-isopropylamine (0.196 ml, 1.4 mmol) in anhydrous THF (2.5 ml) at 0 °C under dry nitrogen. After 5 min, the LDA solution was cooled to -78 °C, and a solution of (305) (366 mg, 1 mmol) in anhydrous THF (2.5 ml) was added dropwise, forming a dark green solution. The mixture was stirred and allowed to warm to -40 °C over *ca.* 1.5 h, and maintained at this temperature for 30 min. After 30 min, the reaction mixture was re-cooled to -78 °C.

The electrophilic reagent (1.1 mmol) was then added dropwise to the mixture, which was stirred for 10 min, and then allowed to warm to room temperature. During this time the colour of the solution changed from a dark green, through dark red, to a transparent dark orange.

The reaction mixture was quenched with saturated ammonium chloride solution (3 ml), poured into water (25 ml) and extracted with ethyl acetate (2 x 25 ml). The organic extracts were combined, washed with brine (25 ml), dried (Na_2SO_4) and rotary evaporated. The resultant dark orange oil was pre-adsorbed onto silica gel and purified by flash column chromatography and, in some cases, by radial chromatography, to yield the product as a pale yellow oil.

Reactions of the lithium ketene thioacetalide (306)

1,1,3-Tris(phenylthio)-1-butene [(307a), E = CH_3] from (306) and iodomethane

Iodomethane (0.07 ml, 1.1 mmol) was added to (306) at -78 °C, and the reaction mixture allowed to warm to room temperature.

After isolation, the dark orange oil was purified by flash column chromatography to yield a yellow oil (307a) (312 mg, 82%):[229] IR (thin film) 2920, 1580, 1475, 1440, 1020 cm^{-1}; ^1H NMR δ (100 MHz) 7.55-6.88 (15H, m, SPh), 6.11 (1H, d, J 10 Hz), 4.60 [1H, m, CHC<u>H</u>(SPh)CH_3], 1.32 (3H, d, J 7 Hz); ^{13}C NMR δ 143.35 (β-CH), 133.76-126.82 (SPh), 43.99 [C<u>H</u>CH(Me)SPh], 20.37 (CH_3); MS (C.I.) m/z (relative intensity) 381 (0.3, $M^{+\cdot}$+H), 379 (0.6, $M^{+\cdot}$-H), 365 (0.6, $M^{+\cdot}-CH_3$), 271 (100, $M^{+\cdot}$-SPh), 111 (37), (E.I.) m/z (relative intensity) 271 (100, $M^{+\cdot}$-SPh), m/z calc. for $C_{16}H_{15}S_2$ ($M^{+\cdot}$-SPh) 271.061, found 271.060.

1,1,3-Tris(phenylthio)-1-butene [(307b), E = CH_3] from (306) and dimethyl sulphate

The butene (307a) was also produced cleanly by reaction of (306) with dimethyl sulphate (0.1 ml, 1.1 mmol). Similar work-up procedure, and purification by flash column chromatography (and radial chromatography) afforded (307b) as a pale yellow oil (308 mg, 81%). The product was identical (IR, NMR and MS analyses) with the material prepared by the procedure involving iodomethane.

3-Trimethylsilyl-1,1,3-tris(phenylthio)-1-propene [(307c), E = $Si(CH_3)_3$] from (306) and chlorotrimethylsilane

Chlorotrimethylsilane (0.13 ml, 1.01 mmol) was added to (306) [337 mg, 0.92 mmol of (305)] in THF at -78 °C. On warming to room temperature, the reaction mixture adopted a transparent, dark orange/red colouration.

After isolation, the resultant oil was purified by flash column chromatography to furnish (307c) (381 mg, 95%): t.l.c. R_f 0.71 (10% ethyl acetate/petroleum); IR (thin film) 3050, 2950, 1575, 1470, 1430, 1240, 1020, 840 cm^{-1}; ^1H NMR δ (100 MHz) 7.50-6.75 (15H, m, SPh), 6.32 (1H, d, J 11 Hz), 4.16 (1H, d, J 11 Hz), 0.20 [9H, s, $Si(CH_3)_3$]; ^{13}C NMR δ 143.73 (β-CH), 131.21-126.66 (SPh), 38.63 [CHCH($SiMe_3$)SPh], -2.38 [$Si(CH_3)_3$]; MS (E.I.) m/z (relative intensity) 438 (1.25, $M^{+\cdot}$), 365 (1.5, $M^{+\cdot}$-$SiMe_3$), 329 (100, $M^{+\cdot}$-SPh), m/z calc. for $C_{24}H_{26}S_3Si$ 438.096, found 438.090.

3-Deuterio-1,1,3-tris(phenylthio)-1-propene [(307d), E = D] from (306) and deuterium oxide

Deuterium oxide (0.044 ml, 2.2 mmol) was added to (306) in THF at -78 °C. Isolation and purification by flash column chromatography afforded a pale yellow oil (307d) (284 mg, 77%). The oil was additionally purified using radial chromatography, eluting with 2% ethyl acetate/petroleum: IR (thin film) 3050, 1580, 1470, 1435, 1020 cm^{-1}; ^1H NMR δ (100 MHz) 7.40-6.94 (15H, m, SPh), 6.15 (1H, quintet, J 3 Hz), 3.82 (1H, d, J 7.5 Hz); ^{13}C NMR δ 135.87-126.82 (β-CH and SPh), 34.56 (CHDSPh); MS (C.I.) m/z (relative intensity) 367 (0.8, $M^{+\cdot}$), 258 (100, $M^{+\cdot}$-SPh), (E.I.) m/z (relative intensity) 258 (100, $M^{+\cdot}$-SPh); m/z calc. for $C_{15}DH_{12}S_2$ ($M^{+\cdot}$-SPh) 258.052, found 258.051.

Formation of the lithium ketene thioacetalide (306) and re-protonation with distilled water (entry e)

The lithium ketene thioacetalide (306) was formed in anhydrous THF at -78 °C under nitrogen as previously described, from 1,1,3-tris(phenylthio)-1-propene (305) (0.28 g, 0.77 mmol) and LDA (0.84 mmol). After allowing the reaction mixture to warm to -40 °C (over 1.5 h), the solution was re-cooled to -78 °C and quenched with excess distilled water. The mixture was allowed to warm to room temperature. Isolation and purification by flash column chromatography afforded a dark orange oil (307e) (241 mg, 86%) which was shown by ^{1}H NMR spectroscopy to have the same structure as (305); no isomerisation was detected by ^{1}H NMR spectroscopy and t.l.c. to the compound reported by McKervey *et al.*[244]

3-Benzyl-1,1,3-tris(phenylthio)-1-propene [(307f), E = $CH_2C_6H_5$] from (306) and benzyl bromide

Benzyl bromide (0.19 g, 0.13 ml, 1.1 mmol) was added to (306) in THF at -78 °C. Isolation and purification by flash column chromatography afforded a red/orange oil (307f) (397 mg, 87%). The oil was additionally purified using radial chromatography, eluting with 1% and then 2% ethyl acetate/petroleum: t.l.c. R_f 0.62 (10% ethyl acetate/petroleum); IR (thin film) 3060, 1580, 1475, 1435, 1020 cm^{-1}; ^{1}H NMR δ (100 MHz) 7.55-6.40 (20H, m, Ph), 6.04 (1H, d, J 10 Hz), 4.77 (1H, ddd, J 10, 5 Hz), 3.13 (1H, dd, J 13, 5 Hz, $C\underline{H}_A H_B Ph$), 2.72 (1H, dd, J 13, 10 Hz, $CH_A \underline{H}_B Ph$); ^{13}C NMR δ 140.85 (β-CH), 137.93 (quaternary C), 134.19 (CH), 133.16, 132.46 (quaternary C atoms), 131.64-126.39 (Ph), 50.44 [$CH\underline{C}H(SPh)CH_2$], 41.01 ($CH_2$); MS (C.I.) m/z (relative intensity) 389 (2.8), 347 (100,

$M^{+\cdot}$-SPh). Anal. calc. for $C_{28}H_{24}S_3$: C, 73.64; H, 5.30. Found: C, 73.3; H, 5.42.

3-Benzyl-1,1,3-tris(phenylthio)-1-propene [(307g), E = $CH_2C_6H_5$] from (306) and benzyl bromide/HMPA

Formation of the ketene thioacetalide (306) in the presence of HMPA (0.52 ml, 3 mmol) (resulting in a very dark red solution), and subsequent reaction with benzyl bromide provided the γ-benzyl compound (390 mg, 85%) after flash column chromatographic purification.

4-Hydroxy-4-phenyl-1,1,3-tris(phenylthio)-1-butene [(307h), E = CH(OH)Ph] from (306) and benzaldehyde

Benzaldehyde (0.11 ml, 1.1 mmol) was added to (306) in THF at -78 °C, and the reaction mixture allowed to warm gradually to room temperature.

After isolation, flash column chromatography afforded the 1:1 mixture of diastereoisomers (307h) (329 mg, 70%) as a dark red/orange oil. Radial chromatography, eluting with 10% ethyl acetate/petroleum, gave the two products as orange oils in the ratio 2:3 (respectively): t.l.c. R_f 0.36 (10% ethyl acetate/petroleum); IR (thin film) 3480 (OH), 3060, 1580, 1475, 1440, 1020 cm^{-1}; ^1H NMR δ (100 MHz) 7.67-6.48 (20H, m, Ph), 6.22 (1H, d, J 10 Hz), 4.94-4.67 [2H, m, CHC<u>H</u>(SPh)CH and C<u>H</u>(OH)Ph], 2.76 (1H, s, OH, exchanges with D_2O), δ (400 MHz) 7.699-6.592 (20H, m, Ph), 6.252 (1H, d, J 10.33 Hz), 4.933 [1H, m, C<u>H</u>(OH)Ph], 4.834 (1H, dd, J 10.31, 3.21 Hz), 2.738 (1H, d, J 2.47 Hz, OH); ^{13}C NMR δ 140.64 (quaternary C), 135.38-126.17 (β-CH and Ph), 73.95 [<u>C</u>H(OH)Ph], 57.80 [CH<u>C</u>H(SPh)CH]; MS (C.I.) m/z (relative intensity) 455 (8.5, $M^{+\cdot}$-OH), 405 (2.1), 363 (92, $M^{+\cdot}$-SPh), 111 (100). Anal. calc. for $C_{28}H_{24}OS_3$: C, 71.15; H, 5.12. Found: C, 70.9; H, 5.50.

t.l.c. R_f 0.29 (10% ethyl acetate/petroleum); IR (thin film) 3480 (OH), 3060, 1580, 1475, 1440, 1020 cm^{-1}; ^1H NMR δ (100 MHz) 7.60-6.45 (20H, m, Ph), 5.83 (1H, d, J 9 Hz), 4.80-4.40 [2H, m, CHC<u>H</u>(SPh)CH and C<u>H</u>(OH)Ph], 3.26 (1H, s, OH, exchanges with D_2O), δ (400 MHz) 7.558-6.546 (20H, m, Ph), 5.842 (1H, d, J 10.43 Hz), 4.685 (1H, dd, J 9.13, 10.43 Hz), 4.568 (1H, dd, J 9.13, 1.50 Hz), 3.213 (1H, d, J 1.88 Hz, OH); ^{13}C NMR δ 140.47 (quaternary C), 136.41 (CH), 135.17 (CH), 133.49, 133.22, 132.89 (all quaternary C atoms), 132.29-127.04 (Ph), 75.36 [<u>C</u>H(OH)Ph], 58.45 [CH<u>C</u>H-(SPh)CH]; MS (C.I.) m/z (relative intensity) 455 (8.5, $M^{+\cdot}$-OH), 405 (2.1), 363 (92, $M^{+\cdot}$-SPh), 111 (100). Anal. calc. for $C_{28}H_{24}OS_3$: C, 71.15; H, 5.12. Found: C, 71.0; H, 5.37.

<u>1,1,3-Tris(phenylthio)hexa-1,5-diene</u> <u>[(307i), E = $CH_2CH{=}CH_2$] from (306) and allyl bromide</u>

Allyl bromide (0.13 g, 0.1 ml, 1.1 mmol) was added to (306) in THF at -78 °C. The reaction mixture was stirred at -78 °C for 10 min, and allowed to warm to room temperature.

The dark red oil obtained on aqueous work-up was purified by flash column chromatography to afford the <u>diene</u> (307i) as a dark red/orange oil (334 mg, 82%); the oil was additionally purified using radial chromatography eluting with 1% and then 2% ethyl acetate/petroleum: IR (thin film) 3080, 1640 (m, C=C), 1580, 1475, 1435, 1020, 920 cm^{-1}; ^1H NMR δ (100 MHz) 7.60-6.85 (15H, m, SPh), 6.08 (1H, d, J 10.5 Hz), 5.75 (1H, m, $CH_2C\underline{H}{=}CH_2$), 5.20-4.90 (2H, m, $CH{=}C\underline{H}_2$), 4.58 [1H, m, CHC<u>H</u>(SPh)-CH_2], 2.70-2.12 (2H, m, CH_2); ^{13}C NMR δ 141.29 (β-CH), 136.84-126.93 (SPh), 117.78 ($CH{=}\underline{C}H_2$), 48.70 [CH<u>C</u>H(SPh)CH_2], 38.95 ($\underline{C}H_2CH{=}CH_2$); MS (E.I.) m/z (relative intensity) 365 (0.8, $M^{+\cdot}$-C_3H_5), 297 (100, $M^{+\cdot}$-SPh), m/z calc. for $C_{18}H_{17}S_2$ ($M^{+\cdot}$-SPh) 297.077, found 297.079.

1,1,3-Tris(phenylthio)-1-pentene [(307j), E = CH_2CH_3] from (306) and iodoethane

Iodoethane (0.17 g, 0.1 ml, 1.1 mmol) was added to (306) in THF at -78 °C, and the reaction mixture allowed to warm to room temperature. T.l.c. analysis of the mixture at ambient temperature revealed a single, new component at a slightly higher R_f value than that of (305).

The dark red oil obtained on aqueous work-up was purified by flash column chromatography eluting with 5% ethyl acetate/petroleum, to afford the pentene (307j) as a dark red/orange oil (378 mg, 96%): IR (thin film) 3060, 2970, 1585, 1475, 1440, 1025 cm^{-1}; ^1H NMR δ (100 MHz) 7.60-6.80 (15H, m, SPh), 6.06 (1H, d, J 10 Hz), 4.40 [1H, m, CHCH(Et)SPh], 1.90-1.45 (2H, broad sextet, CH_2), 0.90 (3H, t, J 7 Hz); ^{13}C NMR δ 142.05 (β-CH), 136.57-126.88 (SPh), 50.76 [CHCH(Et)SPh], 27.79 (CH_2), 11.97 (CH_3); MS (C.I.) m/z (relative intensity) 285 (100, $M^{+\cdot}$-SPh). Anal. calc. for $C_{23}H_{22}S_3$: C, 70.00; H, 5.62. Found: C, 69.6; H, 5.68.

1,1,3-Tris(phenylthio)hepta-1,6-diene [(307k), E = $CH_2CH_2CH{=}CH_2$] from (306) and 4-bromobut-1-ene

4-Bromobut-1-ene (0.15 g, 0.11 ml, 1.1 mmol) was added to (306) in THF at -78 °C. Isolation and purification by flash column chromatography, eluting with 5% ethyl acetate/petroleum, afforded (307k) (309 mg, 74%), appearing at slightly greater R_f value than (305) when examined by t.l.c.: IR (thin film) 3080, 2920, 1640 (m, C=C), 1580, 1475, 1435, 1020, 915 cm^{-1}; ^1H NMR δ (100 MHz) 7.55-6.80 (15H, m, SPh), 6.05 (1H, d, J 10 Hz), 5.67 (1H, m, $CH_2CH{=}CH_2$), 5.17-4.80 (2H, m, $CH{=}CH_2$), 4.52 [1H, m, CHCH(SPh)CH_2], 2.33-1.50 (4H, m, $CH_2CH_2CH{=}CH_2$); ^{13}C NMR δ 141.61 (β-CH), 138.36 ($CH_2CH{=}CH_2$), 137.22-126.99 (SPh), 115.50 ($CH_2CH{=}CH_2$), 48.76 [CHCH(SPh)CH_2], 33.86 (CH_2), 31.31 (CH_2); MS (C.I.) m/z (relative intensity) 421 (4.25,

$M^{+\cdot}+H$), 365 (0.5, $M^{+\cdot}-C_4H_7$), 311 (100, $M^{+\cdot}$-SPh). Anal. calc. for $C_{25}H_{24}S_3$: C, 71.4; H, 5.75. Found: C, 71.2; H, 5.71.

4-Methyl-1,1,3-tris(phenylthio)-1-pentene [(307ℓ), E = $CH(CH_3)_2$] from (306) and 2-bromopropane

2-Bromopropane (0.20 ml, 2.2 mmol) was added to (306) in THF at -78 °C. The reaction mixture was immediately allowed to warm to room temperature.

After isolation, the oil was purified by flash column chromatography, followed by radial chromatography, to afford the pentene (307ℓ) as a very pale yellow oil (170 mg, 42%): t.l.c. R_f 0.63 (5% ethyl acetate/petroleum); IR (thin film) 3060, 2960, 1580, 1475, 1437, 1020, 910 cm^{-1}; ^1H NMR δ (60 MHz) 7.70-6.70 (15H, m, SPh), 6.20 (1H, d, J 10 Hz), 4.37 (1H, dd, J 6, 10 Hz), 2.0 [1H, m, $C\underline{H}(CH_3)_2$], 1.12 (3H, d, J 6.5 Hz), 1.03 (3H, d, J 6.5 Hz); ^{13}C NMR δ 140.58 (β-CH), 133.92-126.88 (SPh), 56.39 [$CH\underline{C}H$-(SPh)CH], 32.83 [$\underline{C}H(CH_3)_2$], 20.86 (CH_3), 19.77 (CH_3); MS (E.I.) m/z (relative intensity) 299 (100, $M^{+\cdot}$-SPh), m/z calc. for $C_{18}H_{19}S_2$ ($M^{+\cdot}$-SPh) 299.093, found 299.093.

3-(1-Hydroxycyclohexyl)-1,1,3-tris(phenylthio)-1-propene [(307m), E = $\overline{C(OH)(CH_2)_4CH_2}$] from (306) and cyclohexanone

Cyclohexanone (0.2 ml, 2.2 mmol) was added to (306) in THF at -78 °C, and the reaction mixture was stirred at this temperature for *ca.* 25 min. The mixture was then quenched with saturated ammonium chloride solution, and the orange solution allowed to warm to room temperature.

After isolation, the resultant oil was purified by flash column chromatography to afford (307m) (431 mg, 93%) as a dark red oil. (307m) was additionally purified by radial chromatography, eluting with 5% then

10% ethyl acetate/petroleum: t.l.c. R_f 0.29 (10% ethyl acetate/petroleum); IR (thin film) 3480 (m, OH), 2930, 1580, 1475, 1436, 975 cm^{-1}; ^1H NMR δ (100 MHz) 7.55-6.68 (15H, m, SPh), 6.33 (1H, d, J 10.5 Hz), 4.57 (1H, d, J 10.5 Hz), 2.15 (1H, s, OH), 1.90-1.18 [10H, m, $(CH_2)_5$]; ^{13}C NMR δ 138.04-126.93 (β-CH and SPh), 73.62 [CHC(OH)], 62.46 [CH(SPh)C$(CH_2)_2$], 36.08, 35.21, 25.57, 21.89, 21.72 [$(CH_2)_5$]; MS (C.I.) m/z (relative intensity) 447 (6, $M^{+\cdot}$-OH), 355 (65, $M^{+\cdot}$-SPh), 339 (24), 111 (100). Anal. calc. for $C_{27}H_{28}OS_3$: C, 69.8; H, 6.07. Found: C, 69.5; H, 6.21.

3-(1-Hydroxycyclopentyl)-1,1,3-tris(phenylthio)-1-propene [(307n), E = $\overbrace{C(OH)(CH_2)_3CH_2}$] from (306) and cyclopentanone

Cyclopentanone (0.2 ml, 2.2 mmol) was added to (306) (2 mmol) in THF at -78 °C, and the reaction mixture was stirred at this temperature for *ca.* 30 min. The mixture was then quenched with saturated ammonium chloride solution, and allowed to warm to room temperature; at which point, the mixture became light orange in colour.

After isolation, the resultant oil was purified by flash column chromatography to yield (307n) [684 mg, 77%; 90% yield when corrected for recovered (305)]: t.l.c. R_f 0.2 (10% ethyl acetate/petroleum); IR (thin film) 3450 (m, OH), 2950, 1580, 1470, 1440, 1020 cm^{-1}; ^1H NMR δ (100 MHz) 7.65-6.75 (15H, m, SPh), 6.38 (1H, d, J 10.5 Hz), 4.64 (1H, d, J 10.5 Hz), 2.32 (1H, s, OH exchanges with D_2O), 2.0-1.47 [8H, m, $(CH_2)_4$]; ^{13}C NMR δ 138.47-126.88 (β-CH and SPh), 83.97 [C(OH)$(CH_2)_2$], 60.68 [CHCH-(SPh)C(OH)], 38.95, 38.08, 23.78 [$(CH_2)_4$]; MS (C.I.) m/z (relative intensity) 433 (8.9, $M^{+\cdot}$-OH), 341 (100, $M^{+\cdot}$-SPh), 325 (36), (E.I.) m/z (relative intensity) 365 (1.5, $M^{+\cdot}$-C_5H_9O), 341 (80, $M^{+\cdot}$-SPh), 77 (100) m/z calc. for $C_{20}H_{21}OS_2$ ($M^{+\cdot}$-SPh) 341.103, found 341.105.

5-Hydroxy-1,1,3-tris(phenylthio)-1-pentene [(307o), E = CH_2CH_2OH] from (306) and ethylene oxide

Excess anhydrous ethylene oxide was admitted into the THF solution of (306) at -78 °C *via* a hypodermic needle. The reaction mixture was stirred at -78 °C for *ca.* 30 min, and allowed to warm to room temperature, during which time the reaction mixture adopted a dark red/orange colouration.

After isolation, the resultant oil was purified by flash column chromatography (1:2 ethyl acetate/petroleum) to afford (307o) (293 mg, 72%). (307o) was additionally purified by radial chromatography (20%, then 30% ethyl acetate/petroleum): t.l.c. R_f 0.48 (1:2 ethyl acetate/petroleum); IR (thin film) 3410 (m, OH), 3060, 1580, 1475, 1025 cm^{-1}; ^1H NMR δ (100 MHz) 7.56-6.78 (15H, m, SPh), 6.04 (1H, d, J 10.5 Hz), 4.67 [1H, m, $CHCH(SPh)CH_2$], 3.79-3.60 (2H, m, CH_2OH), 2.10-1.76 [3H, m, $CH(SPh)CH_2$ and OH, latter exchanges with D_2O]; ^{13}C NMR δ 140.85 (β-CH), 134.35-127.09 (SPh), 60.19 (CH_2OH), 46.27 [$CH(SPh)CH_2$], 37.27 (CH_2CH_2OH); MS (C.I.) m/z (relative intensity) 411 (2.75, $M^{+\cdot}$+H), 301 (100, $M^{+\cdot}$-SPh). Anal. calc. for $C_{23}H_{22}OS_3$: C, 67.3; H, 5.40. Found: C, 67.17; H, 5.52.

7-Chloro-1,1,3-tris(phenylthio)—1-heptene [(307p), E = $CH_2CH_2CH_2CH_2Cl$] from (306) and 1-bromo-4-chlorobutane

To a stirred solution of LDA (3.1 mmol) in anhydrous THF (7 ml) at -78 °C under nitrogen was added dropwise a solution of (305) (1.03 g, 2.8 mmol) in anhydrous THF (7 ml). 1-Bromo-4-chlorobutane (0.53 g, 0.36 ml, 3.1 mmol) was added dropwise, and , on warming to room temperature, the mixture was quenched with saturated ammonium chloride solution (5 ml).

The mixture was poured into water (25 ml) and extracted with ethyl acetate (3 x 20 ml). The organic extracts were combined, brine washed (30 ml), dried (Na_2SO_4) and rotary evaporated. The resultant oil was

purified by flash column chromatography to yield (307p) (1.04 g, 80%). 200 mg were additionally purified by radial chromatography: IR (thin film) 3060, 2940, 1580, 1475, 1435, 1070, 1020 cm^{-1}; ^{1}H NMR δ (100 MHz) 7.52-6.80 (15H, m, SPh), 6.15 (1H, d, J 10 Hz), 4.45 [1H, m, $CHC\underline{H}(SPh)CH_2$], 3.55-3.36 (2H, m, CH_2Cl), 1.95-1.39 [6H, m, $CH(C\underline{H}_2)_3CH_2Cl$]; ^{13}C NMR δ 141.50 (β-CH), 134.03-126.93 (SPh), 48.97 [$C\underline{H}CH(SPh)CH_2$], 44.53 ($CH_2\underline{C}H_2Cl$), 33.75 [$CH(SPh)\underline{C}H_2$], 32.07 ($\underline{C}H_2CH_2Cl$), 24.65 ($CHCH_2\underline{C}H_2$); MS (C.I.) m/z (relative intensity) 423 (0.93, $M^{+\cdot}-^{37}Cl$), 421 (1.75, $M^{+\cdot}-^{35}Cl$), 393 (3.0, $M^{+\cdot}-C_2H_4Cl$), 365 (0.95, $M^{+\cdot}-C_4H_8Cl$), 349/347 (39/75, $M^{+\cdot}$-SPh), 111 (100), (E.I.) m/z (relative intensity) 393 (0.9, $M^{+\cdot}-C_2H_4Cl$), 349 (18, $M^{+\cdot}$-SPh, incorporating ^{37}Cl), 347 (41, $M^{+\cdot}$-SPh, incorporating ^{35}Cl), 117 (100), m/z calc. for $C_{25}H_{25}{}^{35}ClS_3$ 456.081, found 456.080; m/z calc. for $C_{25}H_{25}{}^{37}ClS_3$ 458.078, found 458.076.

3-Methylthio-1,1,3-tris(phenylthio)-1-propene [(307q), E = SMe] from (306) and dimethyl disulphide

Dimethyl disulphide (0.1 g, 0.099 ml, 1.1 mmol) was added dropwise to (306) in THF at -78 °C with no accompanying colour change. The reaction mixture was stirred for *ca.* 10 min, and then allowed to warm to room temperature, producing a very dark red/orange solution.

A strong odour of methanethiol was evident on quenching the mixture with saturated ammonium chloride solution. The organic extracts were also washed with saturated sodium hydrogen carbonate solution (20 ml), brine-washed, dried (Na_2SO_4), and freed of solvent. Purification of the resulting oil by flash column chromatography afforded (307q) (313 mg, 76%; 84% yield when corrected for recovered starting material): t.l.c. R_f 0.53 (5% ethyl acetate/petroleum); IR (thin film) 3060, 2920, 1580, 1470, 1435,

1070, 1020 cm^{-1}; ^1H NMR δ (60 MHz) 7.70-6.90 (15H, m, SPh), 6.07 (1H, d, J 10 Hz), 5.40 (1H, d, J 10 Hz), 2.25 (3H, s, SMe); ^{13}C NMR δ 136.13-127.13 (β-CH and SPh), 53.18 [CHCH(SMe)SPh], 14.48 (SMe); MS (E.I.) m/z (relative intensity) 365 (4.2, $M^{+\cdot}$-SMe), 303 (100, $M^{+\cdot}$-SPh), 255 (25, $C_{15}H_{11}S_2^+$), m/z calc. for $C_{21}H_{17}S_3$ ($M^{+\cdot}$-SMe) 365.049, found 365.045.

1,1,3,3-Tetrakis(phenylthio)-1-propene [(307r), E = SPh] from (306) and diphenyl disulphide

A solution of diphenyl disulphide (0.24 g, 1.1 mmol) in anhydrous THF (2 ml) was added dropwise to (306) at -78 °C, with no accompanying colour change. The reaction mixture was stirred for 10-15 min, and then allowed to warm to ambient temperature, during which time a gradual colour change to a dark red/orange solution was noticed.

A strong odour of thiophenol was noticed on aqueous work-up. The organic extracts were additionally washed with saturated sodium hydrogen carbonate solution (20 ml), and the resulting oil was purified by flash column chromatography to yield (307r) (362 mg, 76%): t.l.c. R_f 0.43 (5% ethyl acetate/petroleum); IR (thin film) 3050, 1580, 1475, 1440, 1065, 1020 cm^{-1}; ^1H NMR δ (100 MHz) 7.65-6.77 (20H, m, SPh), 6.04 (1H, d, J 10.5 Hz), 5.76 (1H, d, J 10.5 Hz); ^{13}C NMR δ 136.09-127.20 (β-CH and SPh), 55.20 [CH(SPh)$_2$]; MS (E.I.) m/z (relative intensity) 365 (100, $M^{+\cdot}$-SPh), 255 (33, m/z 365-PhSH), m/z calc. for $C_{21}H_{17}S_3$ ($M^{+\cdot}$-SPh) 365.049, found 365.045.

4-Hydroxy-7-methyl-1,1,3-tris(phenylthio)octa-1,6-diene [(307s), E = CH(OH)CH$_2$CH=C(Me)$_2$] from (306) and 4-methylpent-3-enal

A solution of 4-methylpent-3-enal[241] (0.11 g, 1.1 mmol) in anhydrous THF (2 ml) was added dropwise to (306) at -78 °C, forming a light orange solution. The reaction mixture was allowed to warm to room temperature.

After isolation, the resultant oil was purified by flash column chromatography to afford the 3:2 mixture of diastereoisomers (307s) [222 mg, 85%; yield corrected for recovered (305)] as an orange oil. The diastereoisomers were additionally purified by radial chromatography eluting with 5% ethyl acetate/petroleum: t.l.c. R_f 0.3 (10% ethyl acetate/petroleum; separation of isomers not evident); IR (thin film) 3470 (m, OH), 2920, 1580, 1475, 1440, 1020 cm^{-1}; ^1H NMR δ (100 MHz) 7.60-6.90 (30H, m, SPh), 6.32 (1H, d, J 10.5 Hz), 6.07 (1H, d, J 10.5 Hz), 5.25-5.0 [2H, m, 2 C<u>H</u>=C(Me)$_2$], 4.73-4.44 [2H, m, 2 CHC<u>H</u>(SPh)CH], 3.92-3.47 (2H, m, 2 C<u>H</u>OH), 2.50-2.12 (6H, m, 2 OH and 2 CH_2), 1.71 (6H, s, 2 CH_3), 1.61 (6H, s, 2 CH_3); ^{13}C NMR δ 137.06-127.09 (β-CH, SPh, and quaternary C atoms), 119.56 [<u>C</u>H=C(Me)$_2$], 119.35 [<u>C</u>H=C(Me)$_2$], 72.81 [<u>C</u>H(OH)CH_2], 72.38 [<u>C</u>H(OH)CH_2], 56.45 [CH<u>C</u>H(SPh)CH], 55.64 [CH<u>C</u>H(SPh)CH], 33.59 (CH_2), 33.43 (CH_2), 25.84 (CH_3), 18.04 (CH_3); MS (C.I.) m/z (relative intensity) 465 (1.45, $M^{+\cdot}$+H), 447 (4.2, $M^{+\cdot}$-OH), 397 (1.65), 355 (100, $M^{+\cdot}$-SPh), (E.I.) m/z (relative intensity) 365 (7, $M^{+\cdot}-C_6H_{11}O$), 355 (47, $M^{+\cdot}$-SPh), m/z calc. for $C_{21}H_{23}OS_2$ ($M^{+\cdot}$-SPh) 355.119, found 355.119.

<u>Attempted alkylation of *1,1,3-Tris(phenylthio)-1-butene* (307a) with LDA/iodomethane</u>

To a solution of distilled di-isopropylamine (0.11 ml, 0.81 mmol) in anhydrous THF (2 ml) at 0 °C under dry nitrogen, was added dropwise *n*-BuLi (0.5 ml, 0.81 mmol, 1.6 M in hexane solution) with stirring. After 5 min, the LDA solution was cooled to -78 °C, and a solution of 1,1,3-tris(phenylthio)-1-butene (307a) (279 mg, 0.73 mmol) in anhydrous THF (2 ml) was added dropwise forming a dark orange/red mixture. The reaction mixture was allowed to warm to -40 °C and stirred at this temperature for 30 min. The mixture was cooled to -78 °C, and iodomethane

(0.05 ml, 0.81 mmol) was added dropwise. The mixture was stirred at -78 °C for 10 min, and allowed to warm to room temperature.

At room temperature, the reaction mixture was analysed by t.l.c. revealing a single component of the same R_f as that of the starting material. The reaction mixture was quenched with saturated ammonium chloride solution (3 ml) and worked up as described previously. ^1H NMR spectroscopy, after flash column chromatography, revealed only starting material present.

Isomerisation of *1,3,3-Tris(phenylthio)-1-propene*[244] (309) to (305) with LDA

To a stirred solution of (309) (20 mg, 0.05 mmol) in anhydrous THF (1 ml) at -78 °C under nitrogen was added a solution of LDA (0.11 mmol) in anhydrous THF (0.22 ml), forming a yellow/green solution. The solution was allowed to warm to -40 °C, and maintained at this temperature for 30 min. After 30 min, the mixture was quenched with saturated ammonium chloride solution (1 ml), and the single product isolated as described previously for the alkylation of (305). The resulting oil was purified by flash chromatography; both t.l.c. and ^1H NMR showed complete conversion of the vinyl sulphide (309) into the ketene thioacetal (305). Physical characteristic NMR for 1,3,3-tris(phenylthio)-1-propene is presented below for comparison with (305): m.p. 83-84 °C (from hexane/acetone); t.l.c. R_f 0.47 (10% ethyl acetate/petroleum); ^1H NMR δ (270 MHz) 7.50-6.98 (15H, m, SPh), 6.13 (1H, d, J 15 Hz, PhSC<u>H</u>), 5.79 (1H, dd, J 15, 8.6 Hz, PhSCH=C<u>H</u>), 4.96 [1H, d, J 8.6 Hz, C<u>H</u>$(SPh)_2$].

(±)-4,5-Dihydro-5-(3-methylbut-2-enyl)-4-(phenylthio)furan-2-(3H)-one [7-methyl-3-(phenylthio)-6-octen-4-olide (312)]

A stirred solution of (307s) (0.53 g, 1.1 mmol) in dichloromethane (10 ml) at room temperature was treated dropwise with TFA (0.88 ml, 10 mmol)

forming a dark orange solution. After *ca.* 20 min, distilled water (8 ml) was added, a strong odour of thiophenol being produced. After stirring for a further 20 min, the mixture was transferred to a separating funnel, and the organic phase was washed with saturated sodium hydrogen carbonate solution (2 x 15 ml), water (15 ml) and dried (Na_2SO_4). After removal of solvent by rotary evaporation *in vacuo*, the residue was dissolved in anhydrous methanol (10 ml) and treated at room temperature with an equal weight of anhydrous sodium hydrogen carbonate. The mixture was stirred vigorously for 15 min, poured into water (10 ml), and extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were washed with water (10 ml), dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography to give on elution with 10% ethyl acetate/petroleum (312) (187 mg, 63%) as an oil: t.l.c. R_f 0.31 (10% ethyl acetate/petroleum); IR ($CHCl_3$) 1780 (vs, C=O) cm^{-1}; ^1H NMR δ (60 MHz) 7.50-7.20 (5H, br s, SPh), 5.01 [1H, br t, J 7 Hz, C<u>H</u>=C(Me)$_2$], 4.33 [1H, q, J 6 Hz, C<u>H</u>(CH_2)O], 3.57 [1H, m, CH_2C<u>H</u>(SPh)CH], 2.90-2.50 (2H, dd, J 11, 8 Hz), 2.50-2.20 (2H, br t, J 7 Hz, C<u>H</u>$_2$CH=C), 1.67 (3H, s, CH_3), 1.55 (3H, s, CH_3); ^{13}C NMR δ 174.23 (C=O), 136.47, 134.41 (both quaternary C atoms), 133.16-128.39 (SPh), 116.91 (CH_2<u>C</u>H=CMe_2), 84.78 [C<u>H</u>CH(CH_2)O], 45.40 [CH_2<u>C</u>H(SPh)CH], 35.81, 32.02 (both CH_2), 25.73, 17.93 (both CH_3); MS (E.I.) m/z (relative intensity) 262 (100, $M^{+\cdot}$), 234 (29, $M^{+\cdot}$-CO), 193 (35, $M^{+\cdot}$-C_5H_9), 180 (18), 152 (20, $M^{+\cdot}$-PhSH), m/z calc. for $C_{15}H_{18}O_2S$ 262.103, found 262.102.

<u>7-Methylocta-2,6-dien-4-olide</u> <u>[(±)-313]</u>[252f]

A stirred solution of (312) (222 mg, 0.85 mmol) in dichloromethane (10 ml) cooled to 0 °C (ice/salt bath) was treated dropwise with DBU (0.14 ml, 0.93 mmol) forming a dark orange solution. The mixture was stirred for *ca.* 30 min, and then 1 M aqueous HCl (5 ml) was added. The mixture was transferred to a separating funnel, and the organic phase was

washed with 1 M aqueous HCl (10 ml), water (10 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* was followed by radial chromatography which gave, on elution with 10% ethyl acetate/petroleum (313) [58 mg, 45%; 60% yield from (307s)], a very pale yellow oil: t.l.c. R_f 0.23 (20% ethyl acetate/petroleum). Physical characteristic IR, ^1H NMR, and optical rotation have been reported previously.[252f] ^{13}C NMR and MS analyses were not included, and are presented below: ^{13}C NMR δ 172.82 (C=O), 156.13 (CH=CHCO), 136.68 (CMe_2), 121.78, 116.47 (both vinyl C atoms), 83.10 [CHCH(CH_2)O], 31.96 (CH_2), 25.79, 17.93 (both CH_3); MS (E.I.) m/z (relative intensity) 152 (10, $M^{+\cdot}$), 69 (100), m/z calc. for $C_9H_{12}O_2$ 152.084, found 152.081.

trans-*3,7-Dimethyl-6-octen-4-olide* [(±)-Eldanolide [251-2], (±)-314]

A solution of methyl-lithium in diethyl ether (1.25 ml, 2.0 mmol, 1.6 M solution) was added dropwise to a stirred suspension of cuprous iodide (0.19 g, 1.02 mmol) in anhydrous diethyl ether (10 ml) cooled to -25 °C under nitrogen, forming an opaque yellow mixture. A solution of the enone (±)-(313) (58 mg, 0.4 mmol) in anhydrous diethyl ether (5 ml) was added dropwise to the cooled solution over *ca.* 5 min, and the mixture was stirred at -25 °C for 1 h.[264]

The mixture was allowed to warm to room temperature and stirred for 30 min, re-cooled to 0 °C and 1 M aqueous HCl (5 ml) was added. The mixture was extracted with diethyl ether (3 x 15 ml), and the combined organic extracts washed with brine (20 ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography to afford (±)-(314) (37 mg, 60%). (±)-(314) was additionally purified by radial chromatography, eluting with 10% ethyl acetate/petroleum: t.l.c. R_f 0.39 (20% ethyl acetate/petroleum); IR ($CHCl_3$) 1770 (vs, C=O) cm^{-1}; ^1H NMR δ (400 MHz) 5.157 (1H, t of septets, J 7.30, 1.44 Hz, $CH_2CH{=}CMe_2$),

4.043 [1H, ddd, J 6.68, 5.41 Hz, $CHC\underline{H}(CH_2)O$], 2.660 (1H, dd, J 16.84, 7.78 Hz, $C\underline{H}_A H_B CO_2$), 2.426-2.301 (2H, m, $C\underline{H}_2CH{=}CMe_2$), 2.289-2.199 (1H, m, $C\underline{H}CH_3$), 2.161 (1H, dd, J 16.83, 9.14 Hz, $CH_A\underline{H}_B CO_2$), 1.712 (3H, d, J 1.13 Hz, $CH{=}C(CH_3^A)C\underline{H}_3^B$), 1.624 [3H, s, $CH{=}C(C\underline{H}_3^A)CH_3^B$], 1.120 (3H, d, J 6.55 Hz, $CHC\underline{H}_3$). The ^{1}H NMR data of this compound are identical with data reported.[252f,g,i-k]

5,6-Dihydro-2H-pyran-2-one[267] (319)

A stirred solution of (307o) (238 mg, 0.58 mmol) in dichloromethane (5 ml) at room temperature was treated dropwise with TFA (0.3 ml, 3.77 mmol) forming a green solution which gradually darkened to a deep red. After *ca.* 20 min, distilled water (3 ml) was added, a strong odour of thiophenol being produced. After stirring for 5 min, the mixture was transferred to a separating funnel, and the organic phase was washed with saturated sodium hydrogen carbonate solution (2 x 10 ml), water (10 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* was followed by flash chromatography to give on elution with ethyl acetate/petroleum (1:2) 4-(phenylthio)tetrahydro-2-pyranone (318) (43 mg, 36%). Complete physical characterisation was not effected on this intermediate compound.

A stirred solution of (318) (43 mg, 0.21 mmol) in dichloromethane (5 ml) cooled to 0 °C (ice/salt bath) was treated dropwise with DBU (0.034 ml, 0.23 mmol). The mixture was stirred for 10 min, and then allowed to warm to room temperature. The mixture was stirred at room temperature for 30 min, and then 1 M aqueous HCl (3 ml) was added. The organic phase was washed with water (5 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* was followed by flash chromatography to give on elution with ethyl acetate/petroleum (1:1) (319) in quantitative yield [35% yield from (307o)]. Complete physical characteristic IR, NMR, and MS analyses have been reported previously,[267] and were identical to the spectroscopic

analyses obtained for (319).

1-Oxaspiro[4.5]dec-3-en-2-one[113] (99)

A stirred solution of (307m) (50 mg, 0.11 mmol) in dichloromethane (7 ml) cooled to *ca.* -10 °C was treated dropwise with TFA (0.054 ml, 0.7 mmol) forming a light green solution. The reaction mixture was left standing at 0 °C for *ca.* 20 h, and then poured into saturated sodium hydrogen carbonate solution (5 ml). Once separated, the organic phase was washed with saturated sodium hydrogen carbonate solution (3 x 10 ml), water (10 ml), and dried (Na_2SO_4). After removal of the drying agent by filtration, the dichloromethane solution was treated dropwise at room temperature with DBU (0.03 ml, 0.22 mmol), and the mixture stirred for *ca.* 1.5 h. The mixture was poured into 1 M aqueous HCl solution (10 ml), washed with water (10 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* was followed by flash chromatography to give (99) (8 mg, 49%). Complete physical characteristic IR, NMR, and MS analyses have been reported previously,[113] and were identical to the spectroscopic analyses obtained for (99).

1-Oxaspiro[4.4]non-3-en-2-one[113] (113)

A stirred solution of (307n) (100 mg, 0.22 mmol) in dichloromethane (20 ml) cooled to *ca.* -15 °C was treated dropwise with TFA (0.11 ml, 1.4 mmol) forming a pale green solution. The reaction mixture was allowed to stand at -15 °C for *ca.* 20h. The mixture was poured into saturated sodium hydrogen carbonate solution (20 ml) contained in a separating funnel; the organic phase was washed with saturated sodium hydrogen carbonate solution (3 x 25 ml), water (20 ml), and dried (Na_2SO_4). The drying agent was removed by filtration, and the dichloromethane solution was treated at room temperature with DBU (0.07 ml, 0.44 mmol), and stirred for *ca.*

1.5 h. The mixture was poured into 1 M aqueous HCl (20 ml), washed with water (20 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* was followed by flash chromatography to give (113) (17 mg, 55%): t.l.c. R_f 0.36 (20% ethyl acetate/petroleum). Complete physical characteristic IR, NMR, and MS analyses have been reported previously,[113] and were identical to the spectroscopic analyses obtained for (113).

2-(2-Phenylthioethylidene)-1,3-dithiane[269b] (323)

Thiophenol (0.8 g, 0.76 ml, 7.42 mmol) was added dropwise to a stirred solution of α-bromoacrolein (1.0 g, 7.42 mmol) in distilled dichloromethane (40 ml) at 0 °C. After 10 min, $BF_3.OEt_2$ (0.5 ml, 3.72 mmol) was added dropwise forming an opaque, yellow mixture. The mixture was stirred for *ca.* 10 min, and then 1,3-propanedithiol (0.8 g, 0.74 ml, 7.42 mmol) was added dropwise, and stirring continued for 10 min.

The mixture was poured into 10% sodium hydroxide solution (50 ml). The organic layer was separated, and washed with more 10% sodium hydroxide solution (2 x 50 ml). The organic extract was washed with distilled water (50 ml), dried (Na_2SO_4), and the drying agent removed by filtration.

To this light green solution was added DBU (1.1 ml, 7.4 mmol) dropwise at ambient temperature with stirring, forming an orange/yellow solution. After *ca.* 20 min, the mixture was poured into 0.5 M aqueous HCl (50 ml). The organic layer was separated, washed with water, dried (Na_2SO_4), and the solvent evaporated *in vacuo*. Purification of the orange residue by flash column chromatography gave, on elution with petroleum, the ketene thioacetal (323) (1.03 g, 55%) as a pale yellow, mobile oil: t.l.c. R_f 0.5 (10% ethyl acetate/petroleum); IR (thin film) 3050, 2930, 1580, 1480, 1440, and 1420(s), 1275(s), 1240(m), 905(s), 865(m) (all dithiane),[201a,306] 740 (vs, Ph) cm^{-1}; ^1H NMR δ (60 MHz) 7.55-7.0 (5H, m, SPh), 5.95 (1H, t, J 8 Hz), 3.68 (2H, d, J 8 Hz), 3.0-2.50 (4H, m, 2 SCH_2), 2.40-1.85

(2H, m, $CH_2\underline{C}H_2CH_2$); ^{13}C NMR δ 135.65 and 131.21 (both quaternary C), 130.34, 128.66, 127.47, 126.28 (β-CH and SPh), 32.72 ($\underline{C}H_2SPh$), 29.90 (SCH_2), 29.42 (SCH_2), 24.81 ($CH_2\underline{C}H_2CH_2$); MS m/z calc. for $C_6H_9S_2$ ($M^{+\cdot}$-SPh) 145.015, found 145.014.

General Procedure for the Alkylation of *2-(2-Phenylthioethylidene)-1,3-dithiane* (323)

n-BuLi (0.68 ml, 1.08 mmol, 1.6 M in hexane solution) was added dropwise to a stirred solution of di-isopropylamine (0.14 g, 0.19 ml, 1.38 mmol) in anhydrous THF (2.5 ml) at 0 °C under dry nitrogen. After 5 min, the LDA solution was cooled to -78 °C, and a solution of (323) (250 mg, 0.98 mmol) in anhydrous THF (2.5 ml) was added dropwise forming a deep red solution. The mixture was stirred and allowed to warm to -40 °C, and maintained at this temperature for 30 min. After 30 min, the reaction mixture was re-cooled to -78 °C.

The electrophilic reagent (1.1 mmol) was then added dropwise to the mixture, which was stirred for 5 min, and then allowed to warm to room temperature. On quenching the mixture with the electrophile, the colour of the solution changed from a deep red to a transparent orange.

The reaction mixture was quenched with saturated ammonium chloride solution (3 ml), poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The organic extracts were combined, washed with brine (20 ml), dried (Na_2SO_4) and rotary evaporated. The resultant orange oil was pre-adsorbed onto silica gel and purified by flash column chromatography to afford the product as a mixture of α- and γ-isomers. All yields quoted represent isolated yields of both isomers taken together. The mixture was subsequently radially chromatographed to furnish the individual regioisomers, and the ratios in which the isomers were produced are tabulated in the text.

Reactions of the lithium ketene thioacetalide derived from (323)

Reaction of the thioacetalide with chlorotrimethylsilane. Treatment of the ketene thioacetalide with chlorotrimethylsilane (0.12 g, 0.14 ml, 1.1 mmol), and subsequent purification by chromatography gave the isomers (324) and (325) [E = $Si(CH_3)_3$] [120 mg, 44%; corrected for recovered (323)].

2-(2-Phenylthiovinyl)-2-trimethylsilyl-1,3-dithiane (324a): t.l.c. R_f 0.74 (10% ethyl acetate/petroleum); IR (thin film) 2950, 1580, 1480 and 1420 (m), 1275 (m), 1250 (s, $SiMe_3$), 920 (s), 840 (s, $SiMe_3$), 740 (s, Ph) cm^{-1}; ^1H NMR δ (60 MHz) 7.48-6.95 (5H, br s, SPh), 6.48 (1H, d, J 14.5 Hz), 5.97 (1H, d, J 14.5 Hz), 3.42-1.82 [6H, m, $(CH_2)_3$], 0.14 (9H, s, $SiMe_3$); ^{13}C NMR δ 135.92, 129.05, 126.44, 124.49 (all CH), 44.26 [$\underline{C}(SiMe_3)$], 25.41 (CH_2), 24.87 (CH_2), -4.17 ($SiMe_3$); MS (E.I.) m/z (relative intensity) 326 (1.65, $M^{+\cdot}$), 311 (2.5, $M^{+\cdot}-CH_3$), 288 (1.15), 253 (11, $M^{+\cdot}-SiMe_3$), 217 (100, $M^{+\cdot}-SPh$), m/z calc. for $C_{15}H_{22}S_3Si$ 326.065, found 326.067.

2-(2-Phenylthio-2-trimethylsilylethylidene)-1,3-dithiane (325a): M.p. 88-91 °C (from petroleum); t.l.c. R_f 0.64 (10% ethyl acetate/petroleum); IR ($CHCl_3$) 2950, 2900, 1580, 910 (m, dithane), 840 (vs, Ph) cm^{-1}; ^1H NMR δ (60 MHz) 7.49-6.88 (5H, m, SPh), 5.90 (1H, d, J 11 Hz), 3.93 (1H, d, J 11 Hz), 2.91-2.39 (4H, m, 2 SCH_2), 2.39-1.82 (2H, m, CH_2), 0.14 (9H, s, $SiMe_3$); ^{13}C NMR δ 137.17 (quaternary C), 135.65 (β-CH), 129.31, 128.45, 125.58 (all CH, Ph), 35.81 [$\underline{C}H(SiMe_3)SPh$], 31.04 ($SCH_2$), 30.45 ($SCH_2$), 25.52 ($CH_2$), -2.71 ($SiMe_3$); MS, m/z calc. for $C_{15}H_{22}S_3Si$ 326.065, found 326.065. Analysis calc. for $C_{15}H_{22}S_3Si$: C, 55.16; H, 6.79. Found: C, 55.04; H, 6.91.

Reaction of the thioacetalide with benzyl bromide

Treatment of the ketene thioacetalide with benzyl bromide (0.185 g, 0.12 ml, 1.1 mmol) and subsequent purification by chromatography (2% ethyl acetate/petroleum) gave the isomers (324) and (325) (E = $CH_2C_6H_5$) (148 mg, 44%).

2-Benzyl-2-(2-phenylthiovinyl)-1,3-dithiane (324b): T.l.c. R_f 0.5 (10% ethyl acetate/petroleum); IR ($CHCl_3$) 2900, 1580, 1475, 950, 910 cm^{-1}; ^1H NMR δ (100 MHz) 7.37-7.15 (10H, 2 br s, Ph), 6.44 (1H, d, J 15.5 Hz), 5.79 (1H, d, J 15.5 Hz), 3.12 (2H, s, $C\underline{H}_2Ph$), 2.93-2.48 (4H, m, 2 SCH_2), 2.19-1.80 (2H, m, CH_2); ^{13}C NMR δ 134.89, 134.41 (quaternary C atoms), 134.03 (CH), 131.16-126.82 (vinyl CH and Ph), 55.58 (quaternary C, $\underline{C}CH_2Ph$), 48.87 ($\underline{C}H_2Ph$), 27.30 (CH_2), 25.19 (CH_2); MS (C.I.) m/z (relative intensity) 345 (100, $M^{+\cdot}+H$), 253 (86.5, $M^{+\cdot}-C_7H_7$), 235 (43, $M^{+\cdot}-SPh$), (E.I.) m/z (relative intensity) 344 (0.5, $M^{+\cdot}$), 253 (23, $M^{+\cdot}-C_7H_7$), 235 (7, $M^{+\cdot}-SPh$), 145 (100), m/z calc. for $C_{13}H_{15}S_2$ ($M^{+\cdot}-SPh$) 235.061, found 235.063.

2-(2-Benzyl-2-phenylthioethylidene)-1,3-dithiane (325b): IR ($CHCl_3$) 2920, 1600, 1585, 1475, 1420, 1275 (m), 910 (m) cm^{-1}; ^1H NMR δ (100 MHz) 7.56-7.10 (10H, m, Ph), 5.85 (1H, d, J 10.5 Hz), 4.56 [1H, m, $C\underline{H}(SPh)CH_2$], 3.17-2.34 (6H, m, 2 SCH_2 and $C\underline{H}_2Ph$), 2.07-1.81 (2H, m, CH_2); ^{13}C NMR δ 138.31 (quaternary C), 133.97 (CH), 133.38 (CH), 129.31-126.44 (Ph), 48.76 [$\underline{C}H(SPh)CH_2$] 40.96 ($\underline{C}H_2Ph$), 30.28 (SCH_2), 29.79 (SCH_2), 24.97 (CH_2); MS (C.I.) m/z (relative intensity) 345 (5.1, $M^{+\cdot}+H$), 253 (3.1, $M^{+\cdot}-C_7H_7$), 235 (100, $M^{+\cdot}-SPh$), (E.I.) m/z (relative intensity) 253 (7.9, $M^{+\cdot}-C_7H_7$), 235 (100, $M^{+\cdot}-SPh$), m/z calc. for $C_{13}H_{15}S_2$ ($M^{+\cdot}-SPh$) 235.061, found 235.062.

Reaction of the thioacetalide with benzyl bromide/HMPA

Formation of the ketene thioacetalide from (323) (235 mg, 0.93 mmol) and LDA (1.02 mmol), in the presence of HMPA (0.48 ml, 2.78 mmol), and subsequent reaction with benzyl bromide (0.12 ml, 1.02 mmol) provided a 1:1 mixture of α- and γ-alkylated products [128 mg, 44%; corrected for recovered (323)] after chromatography (5% ethyl acetate/petroleum).

Reaction of the thioacetalide with cyclohexanone

Cyclohexanone (0.07 ml, 1.02 mmol) was added to the THF solution of the ketene thioacetalide, formed from (323) (235 mg, 0.93 mmol) and LDA (1.02 mmol), at -78 °C. After 5 min, saturated ammonium chloride solution was added, and the mixture allowed to warm to room temperature. Isolation, and subsequent purification by chromatography (10% ethyl acetate/petroleum) gave the isomers (324) and (325) [E = $\overbrace{C(OH)(CH_2)_4CH_2}$] [185 mg, 66%; corrected for recovered (323)] as an orange oil.

2-(1-Hydroxycyclohexyl)-2-(2-phenylthiovinyl)-1,3-dithiane (324d): t.l.c. R_f 0.39 (10% ethyl acetate/petroleum); IR (thin film) 3500 (s, OH), 2940, 1580, 1480, 1420 (s), 1280 (s), 910 (s), 740 (s) cm^{-1}; ^1H NMR δ (60 MHz) 7.50-7.10 (5H, br s, SPh), 6.78 (1H, d, J 14 Hz), 5.94 (1H, d, J 14 Hz), 3.0-2.62 (4H, m, 2 SCH_2), 2.20-1.30 [13H, m, OH and $(CH_2)_6$]; ^{13}C NMR δ 134.95 (quaternary C), 131.48, 129.86, 129.21, 126.98 (all CH), 77.04 [$\underline{C}(OH)CH_2$], 75.73 (dithiane C-2), 68.26, 32.29, 27.03, 25.73, 25.14, 21.72 (all CH_2); MS (C.I.) m/z (relative intensity) 353 (52, $M^{+\cdot}$+H), 335 (44, $M^{+\cdot}$-OH), 145 (100), (E.I.) m/z (relative intensity) 253 (19, $M^{+\cdot}$-$C_6H_{11}O$), 243 (2, $M^{+\cdot}$-SPh), 145 (100), m/z calc. for $C_{12}H_{13}S_3$ ($M^{+\cdot}$-$C_6H_{11}O$) 253.018, found 253.018.

2-[2-(1-Hydroxycyclohexyl)-2-phenylthioethylidene]-1,3-dithiane (325d): M.p. 100-101 °C (from petroleum); t.l.c. R_f0.32 (10% ethyl acetate/petroleum); IR ($CHCl_3$) 3550, 2925, 2850, 1580, 1440, 970, 910 cm^{-1}; ^1H NMR δ (60 MHz) 7.67-7.03 (5H, m, SPh), 5.99 (1H, d, J 11 Hz), 4.34 (1H, d, J 11 Hz), 2.93-2.35 (4H, m, 2 SCH_2), 2.30-1.30 [13H, m, OH and $(CH_2)_6$]; ^{13}C NMR δ 134.19 (quaternary C), 133.81 (CH), 131.05 (CH), 130. 07 (quaternary C), 128.61, 127.31 (both CH), 73.73 [CHC(OH)$(CH_2)_2$], 60.57 [CHCH(SPh)C], 36.08, 34.94, 30.23, 29.74, 25.57, 24.97, 21.94, 21.78 (all CH_2); MS, m/z calc. for $C_{12}H_{19}OS_2$ ($M^{+\cdot}$-SPh) 243.088, found 243.088. Analysis calc. for $C_{18}H_{24}OS_3$: C, 61.32; H, 6.86. Found: C, 61.78; H, 6.78.

1,1-Bis(phenylthio)-1-propene[272] (326). Both the simple ketene bis(phenylthio)acetal (326), and the experimental details required for its preparation have been previously reported by Cohen *et al.*[229] In our hands, the procedure, using propionic acid (1.85 g, 1.86 ml, 25 mmol), afforded (326) (2.37 g, 37%) as a very pale yellow oil after chromatography. Complete physical characteristic IR, NMR and MS analyses were, however, not included, and are presented below: t.l.c. R_f 0.73 (10% ethyl acetate/petroleum); IR (thin film) 3065, 1580, 1470, 1435, 1070, 1020, 740, 690 cm^{-1}; ^1H NMR δ (60 MHz) 7.40-7.05 (10H, 2 s, SPh), 6.38 (1H, q, J 7 Hz), 1.94 (3H, d, J 7 Hz); ^{13}C NMR δ 138.85 (β-CH), 134.35 (quaternary C), 131.32, 130.07, 128.72, 128.61, 127.20, 126.55 (all CH, SPh), 16.96 (CH_3); MS (E.I.) m/z (relative intensity) 258 (64, $M^{+\cdot}$), 149 (100, $M^{+\cdot}$-SPh), 105 (47), m/z calc. for $C_{15}H_{14}S_2$ 258.053, found 258.052.

General Procedure for the Alkylation of *1,1-Bis(phenylthio)-1-propene* (326)

A solution of (326) (258 mg, 1 mmol) in anhydrous THF (2.5 ml) was added dropwise to a stirred solution of LDA (1.1 mmol) in anhydrous THF (2.5 ml) at -78 °C under nitrogen, forming a red reaction mixture. The

mixture was allowed to warm to -40 °C, and maintained at this temperature for 30 min. After 30 min, the reaction mixture was re-cooled to -78 °C.

The electrophilic reagent (1.1 mmol) was then added dropwise to the mixture, which adopted a plum red colour. The mixture was stirred at -78 °C for 5-15 min, and then either quenched with saturated ammonium chloride solution (3 ml) forming a yellow solution, or allowed to warm to room temperature, it gradually lightening to an orange colour.

The mixture was poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The organic extracts were combined, washed with brine (20 ml), dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was subsequently purified by flash chromatography.

Reactions of the lithium ketene thioacetalide derived from (326)

1,1-Bis(phenylthio)-3-(1-hydroxycyclohexyl)-1-propene (328a). Cyclohexanone (0.11 ml, 1.1 mmol) was added to the thioacetalide, and after *ca.* 5 min, saturated ammonium chloride solution was added. Flash chromatography of the residue gave (328a) [267 mg, 75%; 95% yield corrected for recovered (326)] as a white crystalline solid: m.p. 38-41 °C (from petroleum); t.l.c. R_f 0.09 (5% ethyl acetate/petroleum); IR (Nujol) 3280 cm^{-1}; ^1H NMR δ (60 MHz) 7.34-7.10 (10H, 2 s, SPh), 6.50 (1H, t, J 8 Hz), 2.57 (2H, d, J 8 Hz), 2.20 (1H, br s, OH), 1.70-1.30 [10H, br s, $(CH_2)_5$]; ^{13}C NMR δ 139.39 (β-CH), 134.19, 134.03 (both quaternary C), 131.26, 130.99, 130.29, 128.61, 128.50, 127.09, 126.61 (all CH, SPh), 71.78 [$CH_2\underline{C}(OH)(CH_2)_2$], 43.66, 37.54, 25.46, 25.30, 22.05 (all CH_2); MS (E.I.) m/z (relative intensity) 356 (1.3 $M^{+\cdot}$), 338 (0.65, $M^{+\cdot}-H_2O$), 258 (33, $M^{+\cdot}-C_6H_{11}O$), 43 (100), m/z calc. for $C_{15}H_{13}S_2$ ($M^{+\cdot}-C_6H_{11}O$) 258.053, found 258.051. Analysis calc. for $C_{21}H_{24}OS_2$: C, 70.7; H, 6.79. Found: C, 70.3; H, 6.74.

1,1-Bis(phenylthio)-4-phenyl-1-butene (328b). Benzyl bromide (0.13 ml, 1.1 mmol) was added to the ketene thioacetalide, and after *ca.* 5 min, saturated ammonium chloride solution was added. Flash chromatography of the residue gave (328b) (222 mg, 64%) as an oil: t.l.c. R_f 0.48 (5% ethyl acetate/petroleum); ^{1}H NMR δ (60 MHz) 7.40-7.0 (15H, br s, Ph), 6.28 (1H, t, J 7.5 Hz), 2.90-2.60 [4H, m, $(CH_2)_2$]; ^{13}C NMR δ 142.53 (β-CH), 140.80, 134.08 (both quaternary C), 131.37-125.90 (Ph), 35.05 (CH_2), 32.72 (CH_2); MS (C.I.) m/z (relative intensity) 349 (20, $M^{+\cdot}$+H), 348 (14, $M^{+\cdot}$), 257 (40, $M^{+\cdot}$-CH_2Ph), 239 (100, $M^{+\cdot}$-SPh). Analysis calc. for $C_{22}H_{20}S_2$: C, 75.82; H, 5.78. Found: C, 75.39; H, 6.03.

Reaction of the ketene thioacetalide with benzyl bromide/HMPA

Formation of the ketene thioacetalide from (326) and LDA (1.1 mmol), in the presence of HMPA (0.52 ml, 3 mmol), and subsequent reaction with benzyl bromide (0.13 ml, 1.1 mmol) was seen by ^{1}H NMR to afford solely 1,1-bis(phenylthio)-4-phenyl-1-butene (328c).

Reaction of *1,1-Bis(phenylthio)-1-propene* with LDA/Diphenyl disulphide

A solution of diphenyl disulphide (0.24 g, 1.1 mmol) in anhydrous THF (2 ml) was added to the thioacetalide, and after *ca.* 15 min, the mixture was allowed to warm to room temperature. The mixture was quenched with saturated ammonium chloride solution noticing a strong odour of thiophenol. Evaporation of the organic extracts, *in vacuo*, and purification of the residue by flash chromatography gave 1,1,3-tris(phenylthio)-1-propene (328d) (114 mg, 31%) as a pale yellow oil: t.l.c. R_f 0.47 (5% ethyl acetate/petroleum). Complete physical characteristic IR, NMR [237], and MS anal have already been reported [see (305)].

In addition to the desired ketene thioacetal (328d), one other product was obtained on continued elution, a pale yellow oil (329d) (131 mg, 28%):

t.l.c. R_f 0.40 (5% ethyl acetate/petroleum). Both t.l.c. and NMR confirmed this product to be 1,1,3,3-tetrakis(phenylthio)-1-propene.

1,1-Bis(phenylthio)-3-methylthio-1-propene (328e). A solution of (326) (258 mg, 1 mmol) in anhydrous THF (2.5 ml) was added dropwise to a stirred solution of LDA (1.1 mmol) in anhydrous THF (2.5 ml) at -78 °C under nitrogen, forming a red solution. The mixture was stirred for *ca.* 15 min, and then dimethyl disulphide (0.099 ml, 1.1 mmol) was added dropwise with no accompanying colour change. The reaction mixture was stirred for *ca.* 10 min, and quenched with saturated ammonium chloride solution producing a strong odour of methanethiol. Purification of the residue by flash chromatography after evaporation of the solvent *in vacuo*, afforded (328e) (145 mg, 48%) as a colourless, mobile liquid: t.l.c. R_f 0.79 (10% ethyl acetate/petroleum - after eluting twice); ^{1}H NMR δ (60 MHz) 7.43-7.15 (10H, 2 s, SPh), 6.24 (1H, t, J 8 Hz), 3.45 (2H, d, J 8 Hz), 2.05 (3H, s, SMe); ^{13}C NMR δ 136.21 (β-CH), 133.63, 133.15, 132.85 (quaternary C atoms), 132.38-126.89 (SPh), 33.31 (CH_2), 14.94 (SCH_3); MS (E.I.) m/z (relative intensity) 304 (6, $M^{+\cdot}$), 257 (100, $M^{+\cdot}$-SMe), m/z calc. for $C_{16}H_{16}S_3$ 304.016, found 304.016.

1,1-Bis(phenylthio)-3-trimethylsilyl-1-propene (328f). Chlorotrimethylsilane (0.12 g, 0.14 ml, 1.1 mmol) was added to the ketene thioacetalide, and the mixture was stirred at -78 °C for *ca.* 15 min. After 15 min, the pale yellow solution was allowed to warm to room temperature, and quenched with saturated ammonium chloride solution. Flash chromatography of the resulting residue gave (328f) (217 mg, 66%) as an oil: t.l.c R_f 0.57 (5% ethyl acetate/petroleum); IR (thin film) 2970, 1585, 1480, 1440, 1250 (s, $SiMe_3$), 1140, 1030, 850, 745 (s, Ph) cm^{-1}; ^{1}H NMR δ (100 MHz) 7.45-7.12 (10H, br s, SPh), 6.71 (1H, t, J 9 Hz), 2.14 (2H,

d, J 8 Hz), 0.20 [9H, s, $Si(CH_3)_3$]; ^{13}C NMR δ 145.28 (β-CH), 135.61-124.15 (quaternary C atoms, and SPh), 24.12 (CH_2), -1.38 [$Si(CH_3)_3$]; MS (E.I.) m/z (relative intensity) 330 (85, $M^{+\cdot}$), 221 (100, $M^{+\cdot}$-SPh), m/z calc. for $C_{18}H_{22}S_2Si$ 330.093, found 330.090.

Formation of the lithium ketene thioacetalide, and re-protonation with excess anhydrous methanol

A solution of (326) (258 mg, 1 mmol) in anhydrous THF (2.5 ml) was added dropwise to a stirred solution of LDA (1.1 mmol) in anhydrous THF (2.5 ml) at -78 °C under nitrogen. The mixture was allowed to warm to -40 °C, and maintained at this temperature for *ca.* 15 min. Excess anhydrous methanol was added, and the light yellow solution allowed to warm to room temperature. ^1H NMR spectroscopy, after isolation of the product, revealed exclusive re-protonation at the γ-position to yield the thioacetal (328g).

3,3-Bis(methylthio)-1,1-bis(phenylthio)-1-propene (329e). A solution of (328e) (258 mg, 0.85 mmol) in anhydrous THF (2.5 ml) was added dropwise to a stirred solution of LDA (0.94 mmol) in anhydrous THF (2.5 ml) at -78 °C under nitrogen, forming a dark orange solution. The mixture was stirred at this temperature for *ca.* 30 min, before adding dimethyl disulphide (0.08 ml, 0.94 mmol). The mixture was stirred at -78 °C for a further 15 min, the addition of dimethyl disulphide having caused no observable colour change, and then quenched with saturated ammonium chloride solution, forming a yellow solution.

The mixture was poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The organic extracts were combined, washed with brine (20 ml), dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The yellow residue was pre-adsorbed onto silica gel and purification by flash chromatography gave, on elution with petroleum, (329e) (199 mg, 67%) as a pale

yellow oil: ^{1}H NMR δ (60 MHz) 7.50-7.0 (10H, br s, SPh), 6.11 (1H, d, J 10 Hz), 5.04 (1H, d, J 10 Hz), 2.08 (6H, s, 2 SMe); ^{13}C NMR δ 135.81-127.02 (β-CH, SPh, and quaternary C atoms), 50.91 [CH<u>C</u>H(S Me)$_2$], 13.85 (SMe); MS (E.I.) m/z (relative intensity) 303 (5.8, $M^{+\cdot}$-SMe), 255 (1.8, m/z 303-MeSH), m/z calc. for $C_{16}H_{15}S_3$ ($M^{+\cdot}$-SMe) 302.999, found 302.999.

2-(2-Methylthioethylidene)-1,3-dithiane[220b] (322). A solution of trimethylaluminium (24.3 ml, 48.5 mmol, 2 M in toluene) was diluted with dry, de-gassed dichloromethane (50 ml), cooled to 0 °C under nitrogen, and treated dropwise with 1,3-propanedithiol (2.4 ml, 24 mmol). The cooling bath was removed, and the mixture stirred at room temperature for 1 h, to give the bis(dimethylaluminium)-1,3-propanedithiolate reagent. To the solution of reagent was added a solution of methyl 3-methylthiopropionate[275] (331) (3.25 g, 24 mmol) in dichloromethane (10 ml). The white mixture was left stirring at room temperature for 2 days.

The dark green dichloromethane solution was concentrated by rotary evaporation, the residue diluted with diethyl ether, and a few grams of moist Na_2SO_4 were added, causing frothing accompanied by a gradual colour change through green/brown to a transparent light yellow. The diethyl ether was removed by rotary evaporation, and the resulting yellow oil purified by flash chromatography to afford (322) (1.14 g, 24%) as a mobile, pale yellow oil: t.l.c. R_f 0.57 (10% ethyl acetate/petroleum); ^{1}H NMR δ (60 MHz) 5.93 (1H, t, J 8 Hz), 3.26 (2H, d, J 8 Hz), 3.08-2.80 (4H, m, 2 SC<u>H</u>$_2$), 2.35-1.96 (5H, m, $CH_2C\underline{H}_2CH_2$ and SCH_3; latter signal appears as a singlet at δ 2.06); MS, m/z calc. for $C_6H_9S_2$ ($M^{+\cdot}$-SMe) 145.015, found 145.013.

The ketene thioacetal (322) had also been isolated in another experiment, conducted in a modified way to that used for the preparation of (323) (see below).

Methanethiol (1.7 ml, 7.41 mmol, 4.35 M solution in dichloromethane) was added to a stirred solution of α-bromoacrolein (1.0 g, 7.41 mmol) in dichloromethane (40 ml) cooled to -10 °C. $BF_3.OEt_2$ (0.5 ml, 3.71 mmol) was added dropwise forming an opaque, yellow mixture. After *ca.* 3 min, 1,3-propanedithiol (0.8 g, 0.74 ml, 7.42 mmol) was added dropwise and stirring continued for 5 min.

To this pale orange solution was added dropwise DBU (2.22 ml, 14.8 mmol), without prior isolation of the intermediate bromopropane, forming a light yellow solution. The mixture was allowed to warm to room temperature, and then subjected to the same procedure previously described for the isolation of (323). Purification of the residue by flash chromatography gave (322) (293 mg, 21%) as a pale yellow oil: b.p. 125 °C (0.03 mmHg) (Kugelrohr); some decomposition accompanied distillation.

2-(2-Methylthiovinyl)-2-trimethylsilyl-1,3-dithiane (332a). A solution of (322) (70 mg, 0.36 mmol) in anhydrous THF (1 ml) was added dropwise to a stirred solution of LDA (0.4 mmol) in anhydrous THF (2 ml) at -78 °C under nitrogen, forming a green/yellow solution. The mixture was stirred for *ca.* 30 min, and chlorotrimethylsilane (0.05 ml, 0.4 mmol) was then added, forming a very pale yellow solution. After stirring for a further 15 min, the reaction mixture was quenched at -78 °C with saturated ammonium chloride solution (1 ml). The mixture was poured into water (6 ml) and extracted with ethyl acetate (2 x 5 ml). The organic extracts were combined, washed with brine (5 ml), dried (Na_2SO_4) and the solvent removed by rotary evaporation. The residue was pre-adsorbed onto silica gel and purified by flash column chromatography to give, on elution with 10% ethyl acetate/petroleum, (332a) [48 mg, 50%; 62% yield when corrected for recovered (322)]: t.l.c. R_f 0.63 (10% ethyl acetate/petroleum);

^{1}H NMR δ (60 MHz) 6.44 (1H, d, J 14.5 Hz), 5.55 (1H, d, J 14.5 Hz), 3.36-1.85 [9H, m, $(CH_2)_3$ and SCH_3, latter appears as singlet at δ 2.33], 0.15 [9H, s, $Si(CH_3)_3$]; ^{13}C NMR δ 127.31, 127.07 (vinyl CH's), 44.37 (quaternary C), 25.46, 24.52 (both CH_2), 15.60 (SCH_3), -4.27 [$Si(CH_3)_3$]; MS (E.I.) m/z (relative intensity) 264 (17, $M^{+\cdot}$), 249 (100, $M^{+\cdot}-CH_3$), 217 (12, $M^{+\cdot}-SCH_3$), 191 [38, $M^{+\cdot}-Si(CH_3)_3$], m/z calc. for $C_{10}H_{20}S_3Si$ 264.049, found 264.048.

2-Benzyl-2-(2-methylthiovinyl)-1,3-dithiane[220b] (332b). A solution of (322) (192 mg, 1 mmol) in anhydrous THF (2 ml) was added dropwise to a stirred solution of LDA (1.1 mmol) in anhydrous THF (2.5 ml) at -78 °C under nitrogen, forming a dark green solution. The mixture was stirred for *ca.* 30 min, and benzyl bromide (0.19 g, 0.13 ml, 1.1 mmol) was then added, forming a light yellow solution. After stirring for 30 min, saturated ammonium chloride solution was added, and the mixture was poured into water (10 ml). Extraction with ethyl acetate (2 x 10 ml) was followed by washing the combined extracts with brine (10 ml), drying (Na_2SO_4), and rotary evaporation of the solvent. The residue was pre-adsorbed onto silica gel, and chromatography gave (332b) (97 mg, 34%) as a yellow oil: t.l.c. R_f 0.45 (5% ethyl acetate/petroleum); ^{1}H NMR δ (270 MHz) 7.36-7.22 (5H, m, Ph), 6.38 (1H, d, J 15.0 Hz), 5.26 (1H, d, J 15.0 Hz), 3.11 (2H, s, $C\underline{H}_2Ph$), 3.28-1.83 (9H, m, $(CH_2)_3$, and SCH_3, latter appears at δ 2.25 as a singlet); ^{13}C NMR δ 134.46-126.81 (vinyl CH, Ph), 49.38 ($\underline{C}H_2Ph$), 27.20, 27.15 (SCH_2), 25.27 (CH_2), 14.92 (SCH_3); MS (E.I.) m/z (relative intensity) 282 (1, $M^{+\cdot}$), 235 (2.2, $M^{+\cdot}-SMe$), 191 (42, $M^{+\cdot}-CH_2Ph$), 145 (35), 61 (100), m/z calc. for $C_{13}H_{15}S_2$ ($M^{+\cdot}-SMe$) 235.061, found 235.063.

In addition to the desired dithiane adduct (332b), one other product was obtained. (334) (64%): t.l.c. R_f 0.61 (5% ethyl acetate/petroleum); ^{1}H NMR δ (270 MHz) 7.38-7.08 (10H, m, Ph), 5.12 (1H, t, J 7.6 Hz), 3.53-3.47

(2H, septet, CH_2); ^{13}C NMR δ 141.45, 138.03 (both quaternary C atoms), 129.19, 128.56, 128.33, 127.47, 126.81 (Ph), 55.43 (CHBr), 46.37 (CH_2); MS (E.I.) m/z (relative intensity) 181 (100, $M^{+\cdot}$-Br).

1,1,3-Tris(methylthio)-1-propene[279] (335). A solution of trimethylaluminium (3.13 ml, 6.25 mmol, 2.0 M solution in toluene) was diluted with dry, de-gassed benzene (25 ml) and treated at room temperature under nitrogen, with excess, dried ($CaCl_2$ trap) methanethiol, admitted into the bulk of the solution for 30 min. The mixture was then refluxed for *ca.* 20 h, an opaque gel-like substance forming after *ca.* 20 min.

Methyl 3-methylthiopropionate (0.84 g, 6.25 mmol) was added dropwise to the cooled reaction mixture, and *ca.* 2 h after refluxing had been initiated, a transparent yellow solution was formed. After *ca.* 24 h, the reaction mixture was allowed to cool, and quenched with 10% sodium hydroxide solution (20 ml) producing a lime green solution. The mixture was partitioned between 10% sodium hydroxide solution (10 ml) and diethyl ether (10 ml). The organic layer was washed with 10% sodium hydroxide solution (2 x 10 ml), water (20 ml), dried (Na_2SO_4), and the solvent removed by rotary evaporation *in vacuo*. The residue was purified by flash chromatography to give, on elution with 5% ethyl acetate/petroleum, (335) (144 mg, 13%) as a very pale yellow liquid: b.p. 80 °C (0.025 mmHg) (Kugelrohr); t.l.c. R_f 0.77 (10% ethyl acetate/petroleum); ^1H NMR δ (60 MHz) 5.85 (1H, t, J 8 Hz), 3.44 (2H, d, J 8 Hz), 2.28 (6H, s, 2 SCH_3), 2.05 (3H, s, SCH_3); ^{13}C NMR δ 136.19 (quaternary C), 128.56 (vinyl CH), 32.83 (CH_2), 17.06 (SMe), 16.68 (SMe), 14.63 (SMe); MS m/z calc. for $C_5H_9S_2$ ($M^{+\cdot}$-SMe) 133.015, found 133.013.

In addition to the desired ketene thioacetal (335), one other product was obtained on continued elution, a very pale orange liquid (336) (164 mg, 17%): t.l.c. R_f 0.61 (10% ethyl acetate/petroleum); IR (thin film) 1675 (s, C=O) cm^{-1}; ^1H NMR δ (60 MHz) 2.84 (4H, s, CH_2CH_2), 2.32 (3H, s, $COSCH_3$), 2.12 (3H, s, CH_2SCH_3); ^{13}C NMR δ 197.56 (C=O), 43.48 ($\underline{C}H_2$-$COSCH_3$), 29.34 ($\underline{C}H_2SCH_3$), 15.50 ($\underline{C}H_3SCH_2$), 11.56 ($\underline{C}H_3SCO$); MS (E.I.) m/z (relative intensity) 150 (33, $M^{+\cdot}$), 103 (40, $M^{+\cdot}$-SMe), 75 (44, $M^{+\cdot}$-C_3H_7S), 61 (100). Physical characteristic MS data have been reported previously.[280a]

Reactions of the lithium ketene thioacetalide derived from (335)

Reaction with chlorotrimethylsilane: formation of *3-Trimethylsilyl-1,3,3-tris(methylthio)-1-propene* (337a) and *3-Trimethylsilyl-1,1,3-tris(methylthio)-1-propene* (338a). A solution of (335) (144 mg, 0.8 mmol) in anhydrous THF (2 ml) was added dropwise to a stirred solution of LDA (0.88 mmol) in anhydrous THF (2.5 ml) at -78 °C under nitrogen, forming a lime green solution. After 1.5 h, chlorotrimethylsilane (0.07 ml, 0.88 mmol) was added to the light orange solution, and stirring continued for 30 min. Saturated ammonium chloride solution (3 ml) was then added, and the mixture was poured into water (10 ml) and extracted with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with brine (10 ml) and dried (Na_2SO_4). The residue obtained on rotary evaporation was flash chromatographed to afford a 4:1 mixture of the regio-isomers (337a) and (338a) (69 mg, 35%) respectively, as a pale yellow oil: t.l.c. R_f 0.64 (5% ethyl acetate/petroleum); ^1H NMR δ (270 MHz) 6.15 [1H, d, J 15 Hz, (337a)], 5.78 [1H, d, J 11 Hz, (338a)], 5.27 [1H, d, J 15 Hz, (337a)], 3.49 [1H, d, J 11 Hz, (338a)], 2.21 [3H, s, SMe, (338a)], 2.19 [3H, s, SMe, (337a)], 2.18 [3H, s, SMe (338a)], 1.96 [6H, s, $C(\underline{S}Me)_2SiMe_3$, (337a)], 1.92 [3H, s, $CH(\underline{S}Me)SiMe_3$, (338a)], 0.07 [9H, s, $SiMe_3$, (337a)], 0.01 [9H, s, $SiMe_3$, (338a)]; MS (E.I.) m/z (relative

intensity) 252 (24, $M^{+\cdot}$), 237 (70, $M^{+\cdot}-CH_3$), 205 (17, $M^{+\cdot}-SCH_3$), 179 (10, $M^{+\cdot}-SiMe_3$), 117 (100), m/z calc. for $C_9H_{20}S_3Si$ 252.049, found 252.047.

Reaction with benzyl bromide: formation of *4-Phenyl-1,3,3-tris(methylthio)-1-butene* (337b) and *4-Phenyl-1,1,3-tris(methylthio)-1-butene* (338b)

A solution of (335) (136 mg, 0.76 mmol) in anhydrous THF (2 ml) was added dropwise to a stirred solution of LDA (0.83 mmol) in anhydrous THF (2.5 ml) at -78 °C under nitrogen, forming a very light yellow/green solution. The solution was stirred at -78 °C for *ca.* 30 min, and benzyl bromide (0.098 ml, 0.83 mmol) was added, forming a pale yellow solution. After 30 min, saturated ammonium chloride solution (3 ml) was added, and the mixture was allowed to warm to room temperature. The mixture was poured into water (10 ml) and extracted with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with brine (10 ml) and dried (Na_2SO_4). The residue obtained on rotary evaporation was flash chromatographed to give a 7:3 mixture of the regioisomers (337b) and (338b) (94 mg, 46%) as a very pale yellow, mobile liquid: t.l.c. R_f 0.54 (5% ethyl acetate/petroleum); ^1H NMR δ (60 MHz) 7.48-7.05 (10H, br s, Ph), 6.32 [1H, d, J 15 Hz, (337b)], 5.71 [1H, d, J 10 Hz (338b)], 5.30 [1H, d, J 15 Hz, (337b)], 4.35 [1H, m, CHC<u>H</u>(SMe)CH_2, (338b)], 3.12 [2H, s, C<u>H</u>$_2$Ph, (337b)], 3.30-2.50 [2H, m, C<u>H</u>$_2$Ph, (338b)], 2.30-2.0 (18H, three s, 6 SCH_3); MS, m/z calc. for $C_{13}H_{18}S_3$ 270.057, found 270.062.

In addition to the desired adducts (337b) and (338b), one other product was obtained. (334) (76%): t.l.c. R_f 0.61 (5% ethyl acetate/petroleum); ^1H NMR δ (60 MHz) 7.50-7.00 (10H, 2 br s, Ph), 5.13 (1H, t, J 7.5 Hz), 3.48 (2H, d, J 7.5 Hz); ^{13}C NMR δ 141.45, 138.03 (quaternary C atoms), 129.19, 128.56, 128.33, 127.47, 126.81 (Ph), 55.43 (CHBr), 46.37 (CH_2); MS (E.I.) m/z (relative intensity) 181 (100, $M^{+\cdot}-Br$).

1,1-Bis(ethylthio)-3-methylthio-1-propene (339). A solution of trimethylaluminium (3.13 ml, 6.25 mmol, 2.0 M solution in toluene) was diluted with dry, de-oxygenated benzene (25 ml) and treated at room temperature under nitrogen, with ethanethiol (1.4 ml, 18.9 mmol). The mixture was stirred for *ca.* 10 min, and then heated to reflux, noticing the mixture becoming opaque after 1.5 h.

After refluxing for *ca.* 16 h, the white, gelatinous mixture was allowed to cool, and methyl 3-methylthiopropionate (331) (0.84 g, 6.25 mmol) was added. The mixture was again refluxed for *ca.* 4 h, and after cooling, 10% sodium hydroxide solution (20 ml) was added. The mixture was subjected to the same isolation procedure described previously for the preparation of (335). Purification by flash chromotagraphy, eluting with 5% ethyl acetate/petroleum, gave (339) (533 mg, 41%) as a pale yellow liquid: t.l.c. R_f 0.82 (10% ethyl acetate/petroleum); ^{1}H NMR δ (60 MHz) 6.12 (1H, t, J 8 Hz), 3.43 (2H, d, J 8 Hz), 3.0-2.54 (4H, 2q, J 7.5 Hz), 2.05 (3H, s, SMe), 1.40-1.05 (6H, t, J 7.5 Hz); MS, m/z calc. for $C_8H_{15}S_3$ ($M^{+\cdot}$-H) 207.033, found 207.032.

In addition to the desired ketene dithioacetal (339), one other product was obtained on continued elution, a colourless liquid *3-(Methylthio)-1,1,1-tris(ethylthio)propane* (168 mg, 10%): t.l.c. R_f 0.66 (10% ethyl acetate/petroleum); ^{1}H NMR δ (60 MHz) 3.0-2.55 [10H, m, 3 SCH_2 and $(CH_2)_2$; latter appears at δ 2.75 as a singlet], 2.10 (3H, s, SMe), 1.40-1.10 (9H, t, J 7 Hz, 3 CH_3); MS (C.I.) m/z (relative intensity) 270 (0.25, $M^{+\cdot}$), 223 (10, $M^{+\cdot}$-SMe), 209 (77, $M^{+\cdot}$-SEt), 161 (85), 117 (100). No microanalytical data could be obtained due to decomposition.

S-Ethyl 3-(Methylthio)thiolpropionate (340). A solution of trimethylaluminium (3.13 ml, 6.25 mmol, 2.0 M solution in toluene) was diluted with dry, de-oxygenated dichloromethane (25 ml), cooled to 0 °C under nitrogen, and treated dropwise with ethanethiol (1.4 ml, 18.9 mmol). After addition was completed, the cooling bath was removed and the mixture was stirred at room temperature for 1 h. To the solution was added methyl 3-methylthiopropionate (331) (0.84 g, 6.25 mmol), and the transparent, colourless solution was left stirring at room temperature for 2 days.

The transparent, colourless solution was treated with 10% sodium hydroxide solution (20 ml), and the mixture subjected to the same isolation procedure as that described previously for the preparation of (335). Purification by flash chromatrography, eluting with 10% ethyl acetate/petroleum, gave (340) as a very pale yellow mobile liquid in quantitative yield: t.l.c. R_f 0.58 (10% ethyl acetate/petroleum); IR (thin film) 1670 (s, C=O) cm^{-1}; ^1H NMR δ (60 MHz) 3.10-2.68 [6H, m, $SC\underline{H}_2CH_3$ and $(CH_2)_2$, latter appears at δ 2.82 as a singlet], 2.12 (3H, s, SMe), 1.44-1.09 (3H, t, J 7.5 Hz); MS (E.I.) m/z (relative intensity) 164 (52, $M^{+\cdot}$), 103 (30, $M^{+\cdot}$-SEt), 78 (100), m/z calc. for $C_6H_{12}OS_2$ 164.033, found 164.032.

General procedure for the alkylation of *1,1-Bis(ethylthio)-3-methylthio-1-propene* (339)

A solution of (339) (208 mg, 1 mmol) in anhydrous THF (2.5 ml) was added dropwise to a stirred solution of LDA (1.1 mmol) in anhydrous THF (2.5 ml) at -78 °C under nitrogen, forming a light green/yellow solution. The mixture was stirred for *ca.* 30 min, and then the electrophilic reagent (1.1 mmol) was added dropwise, forming a light yellow/lime-green coloured solution. After stirring for 15 min, saturated ammonium chloride solution (3 ml) was added, and the mixture was allowed to warm to room temperature.

The mixture was poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The organic extracts were combined, washed with brine (20 ml), dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The residue was pre-adsorbed onto silica gel and purified by flash chromatography.

Reactions of the lithium ketene thioacetalide derived from (339)

Reaction with dimethyl disulphide: formation of *1,1-Bis(ethylthio)-3,3-bis(methylthio)-1-propene* (342a) and *3,3-Bis(ethylthio)-1,3-bis(methylthio)-1-propene* (341a). Reaction of the ketene thioacetalide with dimethyl disulphide (0.099 ml, 1.1 mmol), and purification of the residue by chromatography, gave a 4:1 mixture of the regioisomers (342) and (341) (E=SMe) (190 mg, 75%): t.l.c. R_f 0.59 (5% ethyl acetate/petroleum); ^1H NMR δ (60 MHz) 6.53 [1H, d, J 14.5 Hz, (341a)], 5.99 [1H, d, J 10 Hz, (342a)], 5.40 [1H, d, J 14.5 Hz, (341a)], 5.05 [1H, d, J 10 Hz, (342a)], 3.03-2.53 (8H, q, J 7.5 Hz, 4 SCH_2), 2.15 (12H, s, 4 SMe), 1.41-1.07 (12H, t, J 7.5 Hz, 4 CH_3); MS (E.I.) m/z (relative intensity) 207 (100, $M^{+\cdot}$-SMe), 193 [17, $M^{+\cdot}$-SEt, probably arising from (341a)], m/z calc. for $C_8H_{15}S_3$ ($M^{+\cdot}$-SMe) 207.033, found 207.032.

Reaction with iodomethane. Treatment of the ketene thioacetalide with iodomethane (0.068 ml, 1.1 mmol) and subsequent chromatographic purification gave two regioisomers: *1,1-Bis(ethylthio)-3-methylthio-1-butene* (342, E = CH_3) (96 mg, 43%): t.l.c. R_f 0.71 (5% ethyl acetate/petroleum); ^1H NMR δ (270 MHz) 5.92 (1H, d, J 10.0 Hz), 4.15 [1H, m, CHC<u>H</u>(SMe)CH_3], 2.83-2.69 (4H, m, 2 SCH_2), 2.03 (3H, s, SCH_3), 1.29-1.19 (9H, m, 3 CH_3); ^{13}C NMR δ 140.67 (β-CH), 130.31 (quaternary C), 40.66 [C<u>H</u>CH(SMe)CH_3], 27.23, 26.74 (both SCH_2), 20.39 (SCH_3), 14.27, 14.16 (both CH_3); MS (E.I.) m/z (relative intensity) 222 (1, $M^{+\cdot}$), 175 (100, $M^{+\cdot}$-SMe), 113 (41, m/z 175-EtSH), m/z calc. for $C_9H_{18}S_3$ 222.057, found 222.058.

3,3-Bis(ethylthio)-1-methylthio-1-butene (341, E = CH_3) (50 mg, 22%): t.l.c. R_f 0.62 (5% ethyl acetate/petroleum); ^1H NMR δ (270 MHz) 6.32 (1H, d, J 15.0 Hz), 5.42 (1H, d, J 15.0 Hz), 2.62-2.53 (4H, 2q, J 7.5 Hz, 2 SCH_2), 2.27 (3H, s, SMe), 1.71 (3H, s, Me), 1.26-1.20 (6H, t, J 7.5 Hz, 2 CH_3); ^{13}C NMR δ 128.10 (vinyl CH), 125.54 (vinyl CH), 58.26 (quaternary C), 28.70 (SCH_3), 24.26 (CH_2), 14.77, 14.12 (both CH_3); MS (E.I.) m/z (relative intensity) 221 (3, $M^{+\cdot}$-H), 207 (5, $M^{+\cdot}$-CH_3), 175 (41, $M^{+\cdot}$-SMe), 161 (100, $M^{+\cdot}$-SEt), m/z calc. for $C_7H_{13}S_2$ ($M^{+\cdot}$-SEt) 161.046, found 161.046.

3-(Methylthio)methyldithiopropionate[271] (345). To a solution of 3-(methylthio)propionitrile[288] (1.5 g, 14.85 mmol) in anhydrous diethyl ether (60 ml) cooled to 0 °C was added a previously prepared stock solution of anhydrous diethyl ether containing dissolved methanethiol (8.9 ml, 22.3 mmol, 2.5 M solution in diethyl ether). Excess anhydrous hydrogen chloride was admitted into the solution, and the mixture was stirred for *ca.* 15 h. Evaporation of the solvent *in vacuo* from the opaque mixture afforded white crystals of 3-(methylthio)methyl thioimidopropionate hydrochloride, which were mixed with anhydrous pyridine (80 ml) and cooled to 0 °C. Anhydrous hydrogen sulphide was slowly admitted into the solution for *ca.* 1.5 h. Within a short period of time, the mixture developed a lemon yellow colour, as the thioimidate salt began to react, and a precipitate was seen to separate out of solution.

After 1.5 h, ice/water (20 ml) was added causing some frothing. The mixture was poured into concentrated hydrochloric acid (60 ml) in water (30 ml)/crushed ice (60 ml), and extracted with diethyl ether. The organic extracts were combined and washed with 2 M hydrochloric acid solution to remove pyridine, and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* was followed by distillation of the residue to afford

(345) (2.24 g, 90%) as a mobile, orange liquid: b.p. 72 °C (0.3 mmHg); t.l.c. R_f 0.83 (20% ethyl acetate/petroleum); IR (thin film) 2920, 1415, 1200, 1125, 1045 cm^{-1}; ^1H NMR δ (60 MHz) 3.52-2.83 (4H, m, CH_2CH_2), 2.67 [3H, s, C(S)SMe], 2.17 (3H, s, $CH_2\underline{SMe}$); MS (E.I.) m/z (relative intensity) 166 (80, $M^{+\cdot}$), 151 (100, $M^{+\cdot}-CH_3$), 71 (27), 61 (51). Analysis calc. for $C_5H_{10}S_3$: C, 36.11; H, 6.06. Found: C, 36.0; H, 6.00.

3,3-Bis(methylthio)methyldithiopropionate (346). To a solution of methyl 3-(methylthio)dithiopropionate (345) (0.5 g, 3.0 mmol, prepared by the literature method)[271] in anhydrous THF (20 ml) at -78 °C under nitrogen, was added dropwise *n*-BuLi (2.1 ml, 3.31 mmol, 1.6 M solution in hexane) forming a colourless solution. The mixture was allowed to warm to -50 °C and treated with *s*-BuLi (2.9 ml, 3.31 mmol, 1.125 M solution in cyclohexane) forming a deep red solution. The mixture was allowed to warm to -40 °C and stirred for *ca.* 1 h, and then re-cooled to -78 °C. The solution was treated dropwise with dimethyl disulphide (0.3 ml, 3.31 mmol), forming a transparent light green mixture. The mixture was stirred for *ca.* 30 min, and saturated ammonium chloride solution (5 ml) was added.

At room temperature, the orange solution was poured into water (30 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (30 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* and evaporative distillation (Kugelrohr) of the resulting liquid gave (346) (0.512 g, 80%): b.p. 200 °C (0.05 mmHg); t.l.c. R_f 0.69 (5% ethyl acetate/petroleum); IR (thin film) 2910, 1530, 1410, 1200, 1040, 955, 830 cm^{-1}; ^1H NMR δ (60 MHz) 4.53 (1H, t, J 7.5 Hz), 3.44 (2H, d, J 7.5 Hz), 2.71 (3H, s, SMe), 2.19 [6H, s, $CH(SMe)_2$]; MS (E.I.) m/z (relative intensity) 212 (57, $M^{+\cdot}$), 165 (100, $M^{+\cdot}-SMe$), 149 (67, m/z 165-CH_4), 91 (40); m/z calc. for $C_6H_{12}S_4$ 211.982, found 211.980.

1,1,3,3-Tetrakis(methylthio)-1-propene[283] (347). A solution of (346) (419 mg, 1.98 mmol) in anhydrous THF (5 ml) was added dropwise to a stirred solution of LDA (2.37 mmol) in anhydrous THF (15 ml) at -78 °C under nitrogen, forming a red/orange solution. After *ca.* 30 min, the solution was treated with iodomethane (0.14 ml, 2.17 mmol) and stirring continued for 15 min. Saturated ammonium chloride solution (5 ml) was added, and the mixture was allowed to warm to room temperature. The mixture was poured into water (30 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (30 ml) and dried (Na_2SO_4). Rotary evaporation of the solvent was followed by evaporative distillation (Kugelrohr) to afford (347) (390 mg, 87%) as an orange liquid: b.p. 150-200 °C/0.05 mmHg (lit.,[283] 130-140 °C/0.25 mmHg); t.l.c. R_f 0.66 (5% ethyl acetate/petroleum); ^{1}H NMR δ (60 MHz) 5.85 (1H, d, J 10 Hz), 5.13 (1H, d, J 10 Hz), 2.38 (3H, s, SMe), 2.36 (3H, s, SMe), 2.20 [6H, s, CH(SMe)$_2$]; MS m/z calc. for $C_6H_{11}S_3$ ($M^{+\cdot}$-SMe) 179.002, found 179.002.

The ketene thioacetal (347) (52 mg, 76%) was also obtained, in a single-step synthesis, from methyl 3-(methylthio)dithiopropionate (345) (50 mg, 0.3 mmol) following the literature procedure[271] used for the preparation of (346). The procedure was modified in this method: iodomethane (0.021 ml, 0.33 mmol) was substituted for the ammonium chloride solution as the second electrophilic reagent added following dimethyl disulphide (0.03 ml, 0.33 mmol).

2-[2-(1,3-Dithian-2-yl)ethylidene]-1,3-dithiane (350). To a stirred solution of 2-trimethylsilyl-1,3-dithiane[293] (200 mg, 1.04 mmol) in anhydrous THF (2.5 ml) cooled to -10 °C under nitrogen, was added dropwise *n*-BuLi (0.72 ml, 1.14 mmol, 1.6 M solution in hexane), forming a pale yellow solution. The mixture was allowed to warm to 0 °C over

ca. 30 min, and a solution of 2-formyl-1,3-dithiane[294] (154 mg, 1.04 mmol) in anhydrous THF (1 ml) was then added dropwise. The cooling bath was immediately removed, and the mixture was stirred at room temperature for *ca.* 16 h.

Saturated ammonium chloride solution (2 ml) was added; the mixture was poured into water (5 ml) and extracted with ethyl acetate (2 x 5 ml). The combined organic extracts were washed with brine (5 ml), dried (Na_2SO_4), and the solvent removed by evaporation *in vacuo*. The residue was purified using radial chromatography, and gave on elution with 2% ethyl acetate/petroleum (350) (95 mg, 37%; 72% when corrected for recovered 2-trimethylsilyl-1,3-dithiane) as an oil: t.l.c. R_f 0.32 (5% ethyl acetate/petroleum); ^1H NMR δ (60 MHz) 5.82 (1H, d, J 10 Hz), 5.11 (1H, d, J 10 Hz), 3.08-2.62 (8H, m, 4 SCH_2), 2.43-1.74 (4H, m, 2 CH_2); MS (E.I.) m/z (relative intensity) 250 (100, $M^{+\cdot}$), 176 (45, $M^{+\cdot}-C_3H_6S$), 119 (39, $C_4H_7S_2^+$), m/z calc. for $C_9H_{14}S_4$ 249.998, found 249.997.

In addition to the desired ketene thioacetal (350), one other product was obtained after chromatography. (351) (17%): m.p. 154-155 °C (from dichloromethane/petroleum); IR (Nujol) 2910, 1605, 1220, 890 cm^{-1}; ^1H NMR δ (270 MHz) 6.76 (2H, s, 2 CH=C), 2.81-2.73 (8H, m, 4 SCH_2), 2.26-2.17 (4H, m, 2 CH_2); ^{13}C NMR δ 135.26 (vinyl CH), 96.09 (quaternary C atom), 32.61, 31.67 (both SCH_2), 26.89 (CH_2); MS (E.I.) m/z (relative intensity) 277 (100, $M^{+\cdot}-H$), 119 (32, $C_4H_7S_2^+$). Analysis calc. for $C_{10}H_{14}OS_4$: C, 43.13; H, 5.07. Found: C, 43.5; H, 5.48.

General procedure for adduct formation (355a-e)

To a stirred solution of LDA (2 molar equivalents) in anhydrous THF (2-10 ml) cooled to -78 °C under nitrogen, was added dropwise a solution of (350) [1 molar equivalent; see individual examples for details concerning the quantities of (350) used] in anhydrous THF (0.5-5 ml), forming

a yellow/green solution which became a light yellow, opaque mixture after *ca.* 30 min. The mixture was allowed to warm gradually to -50 °C, and was then re-cooled to -78 °C. The mixture was treated with the appropriate electrophilic reagent (1.1 molar equivalents; see individual examples).

The reaction mixture was stirred for *ca.* 30 min, during which time the mixture generally became transparent as it gradually warmed. In the case of (355e), this was only observed once the reaction mixture had been allowed to warm to -44 °C.

Saturated ammonium chloride solution (2-4 ml) was added, the reaction mixture was poured into water (5-10 ml), and extracted twice with ethyl acetate (5-15 ml). The combined organic extracts were dried (Na_2SO_4), and the solvent removed by evaporation *in vacuo*. In all cases, the residue was purified by radial chromatography; the compound was eluted with the solvent system given in the text.

2-[2-(1,3-Dithian-2-yl)propylidene]-1,3-dithiane (355a). (48 mg, 98%): t.l.c. R_f 0.44 (5% ethyl acetate/petroleum); ^1H NMR δ (60 MHz) 6.22 (1H, s, CH=C), 3.10-2.64 (8H, m, 4 SCH_2), 2.30-1.74 (7H, m, 2 CH_2 and CH_3, latter appears at δ 1.84 as a singlet); MS (E.I.) m/z (relative intensity) 264 (55, $M^{+\cdot}$), 190 (32, $M^{+\cdot}-C_3H_6S$), 143 (100), 130 (28), m/z calc. for $C_{10}H_{16}S_4$ 264.013, found 264.011. Prepared from (350) (46.3 mg, 0.18 mmol) and iodomethane (0.01 ml, 0.21 mmol); after flash column chromatography (5%, then 10% ethyl acetate/petroleum).

2-[2-(1,3-Dithian-2-yl)-3-hydroxy-3-phenylpropylidene]-1,3-dithiane (355b). (139.2 mg, 76%): t.l.c. R_f 0.13 (10% ethyl acetate/petroleum); IR (thin film) 3450 cm^{-1}; ^1H NMR δ (60 MHz) 7.62-7.23 (5H, m, Ph), 5.92 (1H, s, CH=C), 5.25 [1H, s, C<u>H</u>(Ph)OH], 3.29 (1H, br s, OH), 3.08-2.74 (8H, m, 4 SCH_2), 2.35-1.90 (4H, m, $2CH_2$); MS (E.I.) m/z

(relative intensity) 356 (0.75, $M^{+\cdot}$), 249 (100, $M^{+\cdot}-C_7H_7O$), m/z calc. for $C_{16}H_{20}OS_4$ 356.039, found 356.036. Prepared from (350) (128.2 mg, 0.51 mmol) and benzaldehyde (0.07 ml, 0.66 mmol); after flash column chromatography (5% - then 10% ethyl acetate/petroleum).

2-[2-(1,3-Dithian-2-yl)-3-hydroxyoctylidene]-1,3-dithiane (355c). (101 mg, 76%): t.l.c. R_f 0.15 (5% ethyl acetate/petroleum); ^1H NMR δ (60 MHz) 5.97 (1H, s, CH=C), 4.05 [1H, br d, $CH_2\underline{C}H(OH)C$], 3.12-2.53 [9H, m, 4 SCH_2 and OH), 2.34-0.64 [15H, m, 2 CH_2 both dithiane, $(CH_2)_4CH_3$]; MS (C.I.) m/z (relative intensity) 351 (47, $M^{+\cdot}+H$), 333 (5, $M^{+\cdot}-OH$), 249 (100, $M^{+\cdot}-C_6H_{13}O$), m/z calc. for $C_{15}H_{26}OS_4$ 350.087, found 350.087. Prepared from (350) (95 mg, 0.38 mmol) and hexanal (0.05 ml, 0.42 mmol); after radial chromatography (5% ethyl acetate/petroleum).

2-[2-(1,3-Dithian-2-yl)-4-hydroxybutylidene]-1,3-dithiane (355d). (108 mg, 61%): t.l.c. R_f 0.25 (30% ethyl acetate/petroleum); ^1H NMR δ (60 MHz) 6.13 (1H, s, CH=C), 3.83 (2H, t, J 6.5 Hz, $\underline{CH_2}OH$), 3.10-2.80 (8H, m, 4 SCH_2), 2.50 (2H, t, J 6.5 Hz, $\underline{CH_2}CH_2OH$), 2.30-1.85 (5H, m, $2CH_2$ and OH); MS (C.I.) m/z (relative intensity) 295 (100, $M^{+\cdot}+H$), 294 (33, $M^{+\cdot}$), 277 (6, $M^{+\cdot}-OH$), 220 (25, $M^{+\cdot}-C_3H_6S$). Analysis calc. for $C_{11}H_{18}OS_4$: C, 44.86; H, 6.16. Found: C, 45.10; H, 6.22. Prepared from (350) (151 mg, 0.60 mmol) and excess, anhydrous ethylene oxide; after radial chromatography (25% ethyl acetate/petroleum).

2-[2-(1,3-Dithian-2-yl)-4-hydroxy-6-phenylhexylidene]-1,3-dithiane (355e). (360 mg, 78%): t.l.c. R_f 0.17 (10% ethyl acetate/petroleum); IR (thin film) 3470 (s, OH), 2925, 1545, 1420, 1275, 1065, 915, 750 cm^{-1}; ^1H NMR δ (270 MHz) 7.305-7.167 (5H, m, Ph), 6.171 (1H, s, CH=C), 4.050 [1H, broad septet, $\underline{C}H(OH)CH_2$], 2.958-2.703 (12H, m, 4 SCH_2 and 2 CH_2), 2.463-1.844 (7H, m, 3 CH_2 and OH); MS (C.I.) m/z (relative intensity) 399 (44, $M^{+\cdot}+H$), 398 (25, $M^{+\cdot}$), 324 (23, $M^{+\cdot}-C_3H_6S$), 91 (100). Analysis calc. for

$C_{19}H_{26}OS_4$: C, 57.24; H, 6.57. Found: C, 57.6; H, 6.68. Prepared from (350) (290 mg, 1.16 mmol) and (2-phenylethyl)oxirane[297] (210 mg, 1.39 mmol); after radial chromatography (15% ethyl acetate/petroleum).

2,4-Bis[2-(1,3-dithianyl)]tetrahydropyran (357). A stirred solution of (355d) (100 mg, 0.34 mmol) in dichloromethane (7 ml) cooled to -18 °C (ice/methanol bath) was treated dropwise with TFA (0.17 ml, 2.21 mmol) forming an orange solution. After 30 min, distilled water (4 ml) was added, forming a light yellow solution. The organic phase was washed with saturated sodium hydrogen carbonate solution (2 x 10 ml), water (10 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo*, followed by radial chromatography, gave on elution with 10% ethyl acetate/petroleum, the desired tricyclic adduct (357) (50 mg, 50%) as transparent, oblong needles after recrystallisation: m.p. 110-112 °C (from Et_2O/petroleum); t.l.c. R_f 0.79 (40% ethyl acetate/petroleum); ^1H NMR δ (270 MHz) 4.05 (2H, t, J 5.3 Hz, CH_2O), 3.33-2.58 (8H, m, 4 SCH_2), 2.55 (2H, s, CCH_2C), 2.20 (2H, t, J 5.3 Hz, $C\underline{H}_2CH_2O$), 2.14-1.91 (4H, m, $2CH_2$); MS (E.I.) m/z (relative intensity) 294 (100, $M^{+\cdot}$), 220 (33, $M^{+\cdot}-C_3H_6S$), 188 (8). Analysis calc. for $C_{11}H_{18}OS_4$: C, 44.86; H, 6.16. Found: C, 44.70; H, 6.30.

2,4-Bis[2-(1,3-dithianyl)]-6-(2-phenylethyl)tetrahydropyran (358). A stirred solution of (355e) (210 mg, 0.53 mmol) in dichloromethane (16 ml) cooled to -17 °C (ice/methanol bath) was treated dropwise with TFA (0.26 ml, 3.26 mmol). The solution quickly turned dark green, but faded to an orange/brown colour within 2 min. After stirring for *ca.* 10-15 min, distilled water (10 ml) was added, and the pink/orange mixture was transferred to a separating funnel. The organic layer was washed with a saturated sodium hydrogen carbonate solution (2 x 20 ml), water (10 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo*, followed by

radial chromatography, gave, on elution with 3% ethyl acetate/petroleum, the tricyclic adduct (358) (179 mg, 85%): m.p. 125-126 °C (from CH_2Cl_2/petroleum); t.l.c. R_f 0.63 (20% ethyl acetate/petroleum); IR (thin film) 2930, 1425, 1275, 1080, 960, 910, 705 cm^{-1}; ^1H NMR δ (270 MHz) 7.32-7.18 (5H, m, Ph), 4.30 [1H, m, $CH_2\underline{C}H(CH_2)O$], 3.55-2.50 (12H, m, 4 SCH_2, $\underline{C}H_2Ph$, and C-CH_2-C), 2.33-2.17 [2H, dd, J 29, 14 Hz, $C\underline{C}H_2CH(CH_2)O$], 2.14-1.75 (6H, m, $2CH_2$ and $\underline{C}H_2CH_2Ph$); MS (E.I.) m/z (relative intensity) 398 (100, $M^{+\cdot}$), 324 (27, $M^{+\cdot}-C_3H_6S$), 291 (14). Analysis calc. for $C_{19}H_{26}OS_4$: C, 57.24; H, 6.57. Found: C, 56.9; H, 6.64.

3,5-Bis[2-(1,3-dithianyl)]-2-phenyltetrahydrofuran (360). A stirred solution of (355b) (35 mg, 0.10 mmol) in dichloromethane (2 ml) cooled to -10 °C (ice/methanol bath) was treated with one drop of TFA forming an orange/yellow solution. After 5 min, saturated sodium hydrogen carbonate solution (2 ml) was added. The organic phase was washed with distilled water (4 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo*, followed by flash column chromatography, gave, on elution with 10% ethyl acetate/petroleum, the tricyclic adduct (360) (22 mg, 63%): m.p. 145-146 °C (from EtOAc/petroleum); t.l.c. R_f 0.51 (20% ethyl acetate/petroleum); IR (thin film) 2920, 1420, 1275, 1025, 950, 750 cm^{-1}; ^1H NMR δ (270 MHz) 7.41-7.36 (5H, m, Ph), 5.28 [1H, s, $C\underline{H}(Ph)O$], 3.64-2.45 (9H, m, dithiane ring protons and CH_AH_B-C-O; H_A appears at δ 3.01 as a d, J 15 Hz; H_B appears at δ 2.81 as a d, J 15 Hz), 2.12-1.75 (5H, m, dithiane ring protons); MS (E.I.) m/z (relative intensity) 356 (3, $M^{+\cdot}$), 250 (80, $M^{+\cdot}-C_7H_6O$), 106 (100). Analysis calc. for $C_{16}H_{20}OS_4$: C, 53.89; H, 5.65. Found: C, 53.55; H, 5.68.

4-[2-(1,3-Dithianyl)]-6-(2-phenylethyl)tetrahydro-2-pyranone (361). A solution of the tricyclic adduct (358) (45 mg, 0.113 mmol) in aqueous 80% acetonitrile (2 ml) was added at 28 °C to an efficiently stirring colourless

solution of mercuric chloride (0.14 g, 0.497 mmol) in the same solvent mixture (2 ml). Powdered calcium carbonate (0.05 g, 0.497 mmol) was added to buffer the reaction mixture near pH 7. The dithiane-mercuric chloride complex separated as a flocculent white precipitate in a pale yellow solution. The mixture was stirred at room temperature for 30 min, and filtered through Celite 535 filter aid; the filter cake was washed thoroughly with 1:1 petroleum/dichloromethane. The organic phase of the filtrate was washed with 5 M aqueous ammonium acetate solution, water, and brine (1 ml each), dried (Na_2SO_4), and freed of solvent. The residue was flash chromatographed to afford, on elution with 30% ethyl acetate/petroleum, the lactone (361) (24 mg, 69%) as a viscous oil: t.l.c. R_f 0.27 (20% ethyl acetate/petroleum); IR (thin film) 1730 (vs, C=O) cm^{-1}; ^1H NMR δ (270 MHz) 7.33-7.19 (5H, m, Ph), 4.63 [1H, dddd, J 11.7, 7.9, 4.5, 3.1 Hz, $CH_aH_e\underline{C}H(CH_AH_B)O$], 3.21 (1H, dd, J 17.0, 2.0 Hz, $\underline{C}H_{A'}H_{B'}CO_2$), 3.05-2.70 (7H, m, $\underline{C}H_2Ph$, 2 SCH_2, $CH_{A'}\underline{H}_{B'}CO_2$; latter appears at δ 2.94 as a doublet, J 17.0 Hz), 2.45 [1H, ddd, J 14.5, 3.1, 2.0 Hz, $CH_a\underline{H}_eCH(CH_2)O$], 2.26 (1H, m, $\underline{C}H_AH_BCH_2Ph$), 2.15-1.86 [4H, m, dithiane CH_2, $\underline{C}H_aH_eCH(CH_A\underline{H}_B)O$; H_a appears at δ 1.94 as a dd, J 14.5, 11.5 Hz]; MS (E.I.) m/z (relative intensity) 308 (100, $M^{+\cdot}$), 234 (15, $M^{+\cdot}-C_3H_6S$), 142 (4.5), 106 (12), m/z calc. for $C_{16}H_{20}O_2S_2$ 308.090, found 308.090.

(±)-5,6-Dihydro-4-methoxy-6-(2-phenylethyl)-2-pyranone [(±)-Dihydrokawain, (±)-362].[309] A solution of the dithiane (361) (37 mg, 0.12 mmol) in acetone (0.5 ml) at 25 °C was added dropwise to a solution of NBS (0.17 g, 0.96 mmol) in aqueous 97% acetone (3 ml) stirring at -5 °C. The addition produced a clear yellow solution; it was stirred for 5 min and shaken with a mixture of saturated aqueous sodium sulphite (1.5 ml) and 1:1 petroleum-dichloromethane (1.5 ml). The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (1.5 ml), water

(1.5 ml) and brine (1.5 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* afforded an opaque residue which was dissolved in acetone (0.5 ml) at 25 °C. To the stirred solution was added powdered, anhydrous potassium carbonate (0.03 g, 0.24 mmol) followed by dimethyl sulphate (0.02 ml, 0.24 mmol), and the mixture stirred for *ca.* 20 h. The mixture was poured into water (1 ml) and ethyl acetate (1 ml), and extracted with ethyl acetate (3 x 1 ml). The combined organic extracts were dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The residue was purified by preparative thin layer chromatography to give, on elution with ethyl acetate/petroleum (1:1), (±)-(362) [8.4 mg, 30%; 15% yield based on amount of (358) used] as colourless needles: m.p. 67-69 °C (lit.[309c] 65-69 °C; lit.[304a] 69-71 °C); t.l.c. R_f 0.49 (1:1 ethyl acetate/petroleum); IR ($CHCl_3$) 1725 (vs, C=O) cm^{-1}; ^1H NMR δ (270 MHz) 7.26 (5H, br s, Ph), 5.14 (1H, d, J 1.6 Hz, $CH=C\underline{H}CO_2$), 4.37 [1H, dddd, J 11.8, 8.2, 4.5, 4.0 Hz, $CH_2C\underline{H}(CH_2)O$; the signal appears as an octet], 3.73 (3H, s, OCH_3), 2.95-2.72 (2H, m, $C\underline{H}_2Ph$), 2.52 [1H, ddd, J 16.9, 11.8, 1.6 Hz, $C\underline{H}_aH_eCH(CH_2)O$], 2.30 [1H, dd, J 16.9, 4.0 Hz, $CH_a\underline{H}_eCH(CH_2)O$], 2.14 (1H, m, $C\underline{H}_AH_BCH_2Ph$), 1.93 (1H, m, $CH_A\underline{H}_BCH_2Ph$); MS (E.I.) m/z (relative intensity) 232 (100, $M^{+\cdot}$), 204 (27), 200 (45, $M^{+\cdot}$-MeOH), 127 (65, $M^{+\cdot}-C_8H_9$), 177 (12). The 270 MHz ^1H NMR spectrum is identical to that previously reported.[304b]

PUBLICATIONS

Tetrahedron Letters,Vol.26,No.37,pp 4547-4550,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

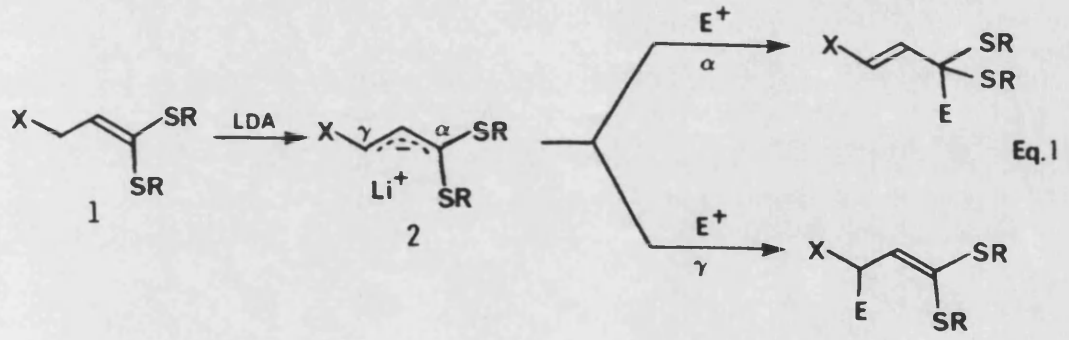
γ-SUBSTITUTED KETENE THIOACETALS AS β-LITHIOACRYLATE EQUIVALENTS. THE SYNTHESIS OF (±)-ELDANOLIDE

Edward Dziadulewicz and Timothy Gallagher*

School of Chemistry, Bath University, BATH BA2 7AY, U.K.

Summary: Lithiation of 1,1-bis(phenylthio)-3-phenylthio-1-propene 3 and reaction with a range of electrophiles gave exclusively the γ-substituted product 4. This reagent has been used in a short synthesis of the pheromone, (±)-eldanolide.

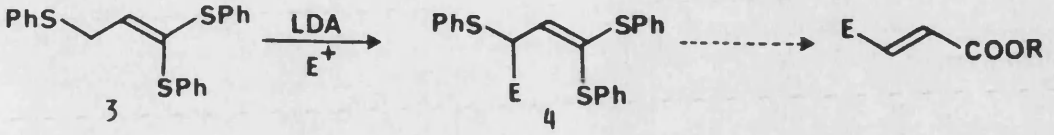
The ready availability of ketene thioacetals has reinforced the role of these compounds as useful synthetic intermediates.[1] A particularly important aspect of their chemistry that has been widely exploited involves lithiation of 1 and reaction of the resulting anion 2 with various electrophiles.



1 2 Eq.1

The synthetic value of this process is controlled by the regioselectivity (α vs γ) of electrophilic attack at this ambident anion. In general alkylation (with RX, Me_3SiCl, also D_2O) takes place at the 'harder' α-site while aldehydes and ketones react predominantly at the 'softer' γ-site. (Eq.1)[2] However this regioselectivity is sensitive to a number of factors one of which is the nature of the substituent (X) at the γ-position of 1.[3]

We now report that incorporation of a γ-phenylthio group into 1 (R=R'=Ph, X=SPh i.e.3) directs both 'hard' and 'soft' electrophiles to the γ-site exclusively. In addition, hydrolysis of the ketene thioacetal moiety and elimination of thiophenol from these adducts (i.e. 4) allows 1,1-bis(phenylthio)-3-phenylthio-1-propene 3 to be regarded as a versatile β-lithioacrylate equivalent.[4]



Preparation of **3** was carried out in two steps, in 83% overall yield, from α-bromoacrolein. Addition of thiophenol (3eq.$PhSH/BF_3{\cdot}Et_2O/CH_2Cl_2$) to α-bromoacrolein followed by elimination of HBr (DBU/CH_2Cl_2) gave **3** as a pale yellow oil which crystallised at -15°C.[5] Lithiation of **3** was carried out using LDA/THF at -78°C. The resultant solution was warmed to -40°C and maintained at this temperature for 30 minutes. The anion solution was then recooled to -78°C and treated with the appropriate electrophile. The reaction mixture was generally allowed to warm to room temperature before addition of aqueous NH_4Cl. When cyclopentanone and cyclohexanone were involved, however, best results were obtained by quenching the reaction mixture at -78°C.

A variety of electrophiles were examined (see Table) and in all cases the γ-regioisomer **4** was the only product isolated.[6]

This regiochemical assignment is based primarily on NMR (^1H and ^{13}C) and, for entries (viii), (ix) and (x), this assignment was confirmed by conversion of the product to the corresponding α,β-unsaturated lactone (**5**, **6** and **7** respectively) using the conditions described below.[7]

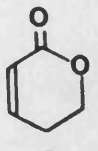
TABLE

Entry	Electrophile	Yield of **4**(%)
(i)	MeI	82[a]
(ii)	$PhCH_2Br$	87[b]
(iii)		82
(iv)		42
(v)	Me_3SiCl	95
(vi)	D_2O	88
(vii)	PhCHO	70[c]
(viii)		72
(ix)	cyclopentanone	70[d]
(x)	cyclohexanone	93

a. Use of $(MeO)_2SO_2$ gave **4** (E=Me) in 81% yield.
b. Alkylation in the presence of HMPA still gave the γ-regioisomer as the sole product.
c. Obtained as a 3:2 mixture of diastereoisomers.
d. Unlike cyclohexanone, cyclopentanone has been shown to react preferentially at the α-site.[2]

Entries (v) and (vi) are of particular interest. Even in systems that show a preference for γ alkylation (e.g. **1** R/R'=$(CH_2)_3$, X=Ph) these two electrophiles (Me_3SiCl and D_2O) still react

exclusively at the α-position.[3] Benzylation of **3** is also significant (entry (ii)). Studies on a closely related system **8** by Corey and Kozikowski have shown that, in this case, the α-benzylated regioisomer was formed.[8] Clearly further investigation is necessary to more accurately define the factors influencing α vs γ selectivity in carbanions of this type.



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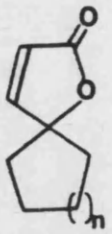
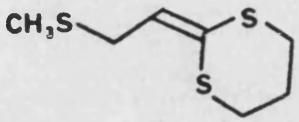


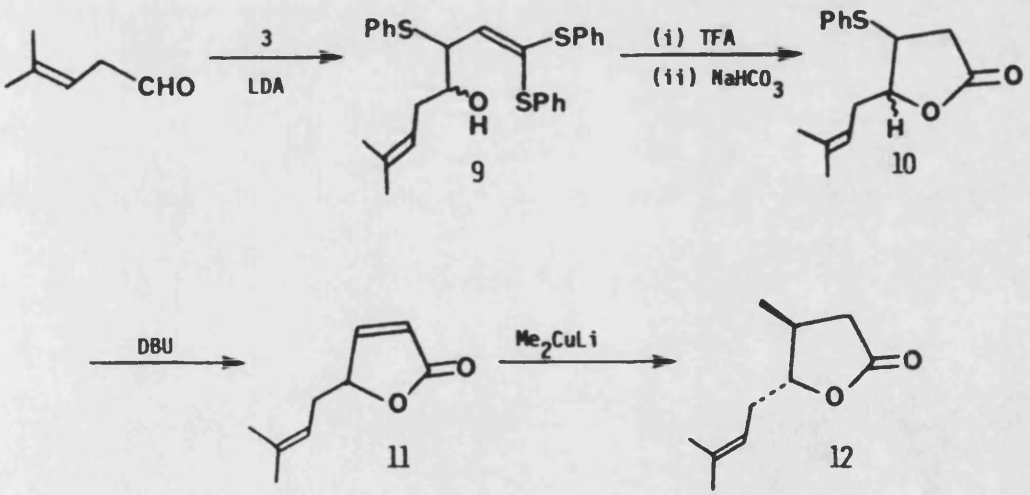
6 n = 1
7 n = 2



8

The use of **3** as a β-lithioacrylate equivalent is exemplified here by a short synthesis of (±)-eldanolide **11**, the wing gland pheromone of *Eldana saccharina* (wlk).[9] Treatment of the lithio derivative of **3** with 4-methyl-3-pentenal[10] gave alcohol **9** (85%) as a mixture of diastereoisomers. Lactonisation of **9** (TFA/CH_2Cl_2 followed by $NaHCO_3/H_2O$/MeOH) and subsequent elimination of thiophenol from lactone **10** (DBU/CH_2Cl_2) gave butenolide **11** (60% yield from **9**). This compound has been previously reported and was converted to (±)-eldanolide **12** (Me_2CuLi, 60%) as described by Kunesch *et al.*[9d] (see Scheme).

SCHEME



Acknowledgement: SERC is thanked for their support of this work.

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5. **4**: ^{1}H NMR δ($CDCl_3$) 7.3-6.7(15H,m), 6.06(1H,t,J=7.5Hz), 3.76(2H,d,J=7.5Hz). Although this material decomposed on attempted distillation it was easily purified by filtration through silica gel.
6. Satisfactory i.r., n.m.r. (^{1}H and ^{13}C) and high resolution mass spectral data were obtained for all new compounds. In general adducts **4**, which were all obtained as colourless or pale yellow oils, decomposed on attempted distillation. Purification was readily effected by chromatography over silica gel and all yields quoted are of purified products.
7. Spectral data (i.r. and n.m.r.) for spirolactones **6** and **7** were consistent with the assigned structures. See P. Canonne, D. Bélanger and G. Lemay, *J. Org. Chem.*, **47**, 3953, (1982).
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(Received in UK 10 July 1985)

Tetrahedron Letters, Vol. 28, 1987: in press.

POLYFUNCTIONAL KETENE THIOACETALS
SYNTHESIS OF A β-LITHIO β-HYDROXYACRYLATE EQUIVALENT

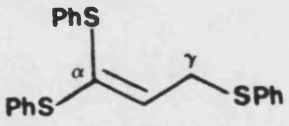
EDWARD DZIADULEWICZ, MELVYN GILES AND TIMOTHY GALLAGHER*

School of Chemistry, University of Bath,
Claverton Down, Bath BA2 7AY, U.K.

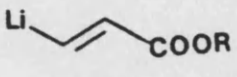
Summary: The synthesis of ketene thioacetal (3) is reported. Deprotonation of (3) generates anion (4) and the equivalence of this species to a β-lithio β-hydroxyacrylate (5) has been demonstrated.

The application of ketene thioacetals to the stabilisation of allylic anions and, to a lesser extent, their use as a protected form of a carboxylic acid is now well established.[1] Although most efforts in this area have focussed on the reactions of relatively simple ketene thioacetals, the value of this group may be extended by developing the chemistry of more highly functionalised variants.

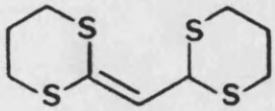
With this objective in mind, we prepared the γ-substituted ketene thioacetal (1).[2] Deprotonation of (1) provides an allylic anion which reacts with a wide range of electrophiles exclusively at the γ-site, and may be regarded as synthetically equivalent to a β-lithioacrylate (2).



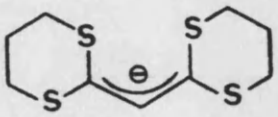
(1)



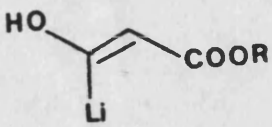
(2)



(3)



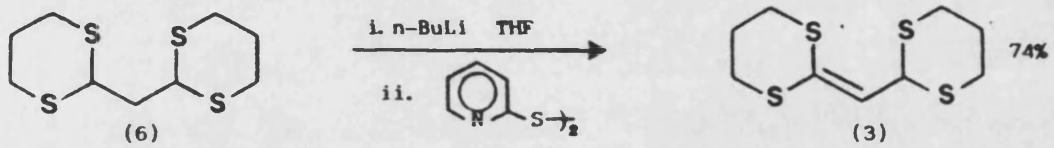
(4)



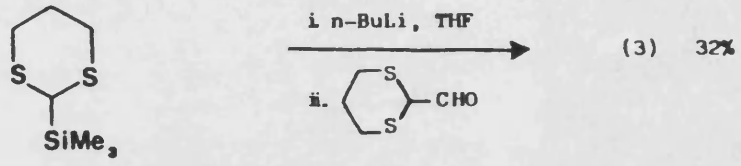
(5)

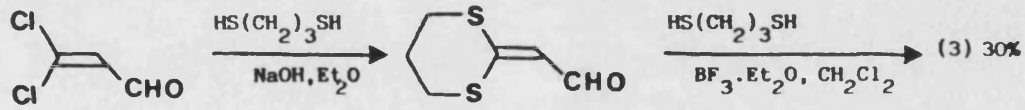
We now wish to describe the synthesis of the novel bis(dithiane)(3), deprotonation of which gives the symmetrical anion (4) which behaves as a functional equivalent of a β-lithio β-hydroxyacrylate (5).[3] There has been considerable interest in anions related to (5), with a particular emphasis on their use in the synthesis of tetronic acids and related systems.[4]

Various approaches to (3) have been evaluated, and are shown below. The most efficient synthesis of (3)[5] [74% yield from (6)[6]] was based on Fujita's[7] elegant method for the preparation of ketene thioacetals. Two other routes were examined but proved to be less useful. The major problem in the Peterson-based approach was self-condensation of 2-formyl-1,3-dithiane.3,3-Dichloro-2-propenal[8] also represents a readily available precursor of (3), and although the first condensation step to give (7) proceeded in essentially quantitative yield, the subsequent thioacetalation was less efficient.



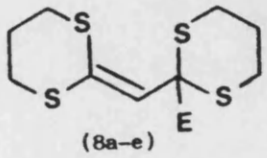
(6) (3)



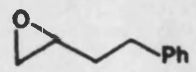
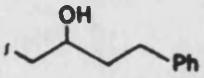
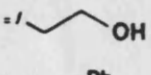
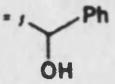
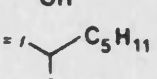


(7)

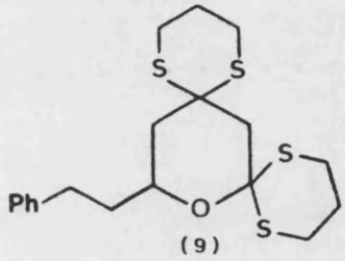
Metallation of (3) was achieved under standard conditions [LDA,THF,-78°C to -40°C,1hr] and the anion (4) was trapped, at -78°C, by a variety of electrophiles to give adducts (8a-e) in synthetically useful yields.



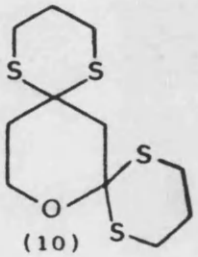
(8a-e)

Electrophile	(8) (% yield)
	a E =  78%
	b E =  61%
PhCHO	c E =  76%
$C_5H_{11}CHO$	d E =  76%
MeI	e E = —Me 98%

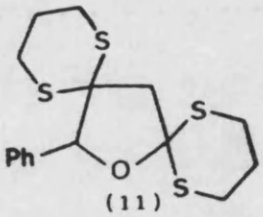
The acid-catalysed cyclisation[9] [CF_3CO_2H,CH_2Cl_2] of alcohols (**8a–c**) proceeded smoothly to give the doubly protected β-ketolactones (**9**), (**10**) and (**11**) in 85%, 50% and 62% yield respectively. Hydrolysis of these heterocycles should enable the release of both carbonyl functions, thereby demonstrating the synthetic equivalence of (**3**) to a β-lithio β-hydroxy-acrylate (**5**).



(9)



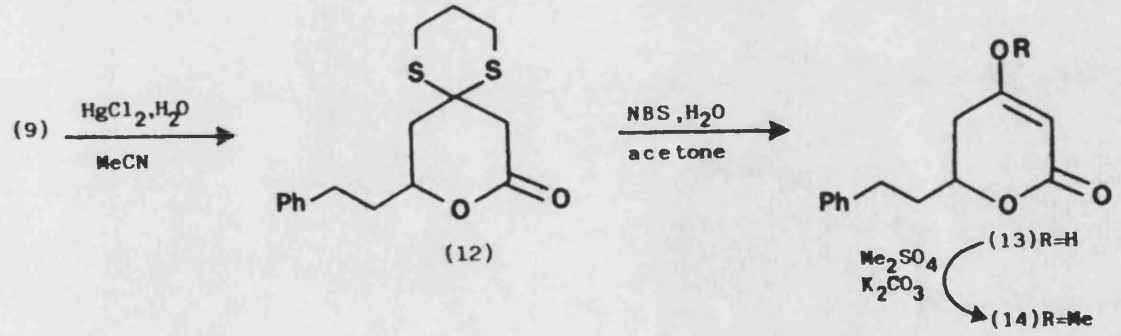
(10)



(11)

Under appropriate conditions these two carbonyl functions may be liberated in a step-wise fashion. This has been illustrated below using (**9**) as an example, and the sequence validated by correlation with (±)-dihydrokawain (**14**), a compound that has been previously described.[10]

Mild hydrolysis of (**9**) [H_2O,Me–CN,$HgCl_2$] gave lactone (**12**) in 69% yield. Further reaction of this intermediate, under more vigorous conditions [NBS,Me_2CO,H_2O],[11] gave (**13**) which was methylated [Me_2SO_4,Me_2CO,K_2CO_3] in situ to provide (**14**) [m.p. 67–69°C, lit.[10], 69–71°C] in 30% overall yield from (**12**).



Acknowledgements: SERC and Bath University are thanked for their generous financial support of this work.

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224. Metalation of 298 (x=1) with 1 eq. n-BuLi or 1 eq. LDA at -78°C and reaction with benzyl bromide, deuterium oxide or iodomethane afforded no recognisable alkylation products. It is known that 1,3-dithiolanes can undergo C-4 metalation and subsequent dithiolane ring fragmentation (a), although 2-alkyl-1,3-dithiolanes have been reported to undergo metalation, exchanging the 2-H 19 times faster than 1,3-dithianes (b). (a) S. R. Wilson, G.M. Georgiadis, H.N. Khatri and J.E. Bartmess, J. Am. Chem. Soc., (1980),

102, 3577; S.R. Wilson, P. Caldera and M.A. Jester, J. Org. Chem., (1982), 47, 3319; (b) S. Oae, W. Tagaki and A. Ohno, Tetrahedron, (1964), 20, 417, 427.

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227. Preparations of dithioacetals from aldehydes are often more efficiently carried out by first converting the starting material into an acetal : E.J. Corey and D. Seebach, Org. Synth., (1970), 50, 72; E.L. Eliel and A.A. Hartmann, J. Org. Chem., (1972), 37, 505. See also ref. 232.

228. Compound 301 resembles the 1,3-dianion equivalent described by Otera et al. in ref. 127, but incorporating a C-2 synthetic handle.

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above ref. and the accompanying paper, p. 3601.

230. This was found not to be the case when α-bromoacrolein was reacted under similar conditions, but this was not pursued.

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234. All enone examples in the references listed under 223 were disubstituted at C-3. With C-3 unhindered enones, thiols behave in a manner seen in : P. Bakuzis and M.L.F. Bakuzis, J. Org. Chem., (1981), 46, 235; see also formation of compound 128, ref. 123.

235. a) A similar preparative procedure has been previously employed, see : ref. 201a) p. 671, Route C and associated references; ref. 283; K. Tanaka, T. Nakai and N. Ishikawa, Chem. Lett., (1979), 175; J.A. Marshall and J.L. Belletire, Tetrahedron Lett., (1977), 871. For a synthesis of vinyl sulphides : B. Giese and S. Lachhein, Chem. Ber., (1979), 112, 2503; b) In the absence of a C-2 leaving group, 304 would react with base to form 1,1-bis(phenylthio)cyclopropane : T. Cohen, W.M. Daniewski, and R.B. Weisenfeld, Tetrahedron Lett., (1978), 4665 and ref. 2 cited therein; T. Cohen and W.M. Daniewski, ibid., (1978), 2991 and ref. 1 and 2 cited therein; T. Cohen,

J.P. Sherbine, S. A. Mendelson and M. Myers, ibid., (1985), 26, 2965.

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237. E.K. Dziadulewicz and T.C. Gallagher, Tetrahedron Lett., (1985), 26, 4547.

238. The general procedure followed : D. Seebach, Synthesis, (1969), 17; see also refs. 202h) and 220b), although in latter case HMPA was included. The cosolvent was omitted by us.

239. Personal communication : D.M. Hodgson, undergraduate project report no. 355., University of Bath, 1986, for B.Sc in Chemistry.

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241. M. Julia and G. Le Thuillier, Bull. Soc. Chim. Fr., (1966), 717.

242. a) see ref. 221c); b) see ref. 221e); c) D. Seebach, M. Kolb and B-T. Gröbel, Chem. Ber., (1973), 106, 2277.

243. The only ^{13}C NMR data available on ketene dithioacetals were measured on 2-alkylidene-1,3-dithiane derivatives: see ref. 201a).

244. J.P. Cronin, B.M. Dilworth and M.A. McKervey, Tetrahedron Lett., (1986), 27, 757.

245. This was judged arbitrarily on the basis of the model procedures listed in ref. 238. Ref. 202h) specified warming to +20°C within 2-3 hr. whereas 220b) suggested warming to -40°C over 90 min., and maintaining this temperature for an additional 30 min.

246. The oxidative coupling of dithiane anions is known: E.J. Corey and D. Seebach, Angew. Chem., Int. Ed. Engl., (1965), 4, 1077; the coupling of ketene dithioacetalides has been previously observed : ref. 221c).

247. P. Freche, A. Gorgues and E. Levas, Tetrahedron, (1977), 33, 2069. α -Oxoketenedithioacetals have been recently shown to have many useful applications : R.K. Dieter, Tetrahedron, (1986), 42, 3029 (review).

248. This was recognised by Kozikowski et al. but not developed : see ref. 221a).

249. The γ -lactone ring system is a common feature in a wide variety of natural products, and a number of methods are available for its construction : ref. 10a).

250. Head-to-tail dimerisation of isoprene units and incorporation of carbon dioxide.

251. G. Kunesch, P. Zagatti, J.Y. Lallemand, A. Debal and J.P. Vigneron, Tetrahedron Lett., (1981), 22, 5271.

252. a) ref. 178; b) ref. 237; c) J.-M. Fang and B.-C. Hong, Synth. Commun., (1986), 16, 523; d) ref. 251; e) J.P. Vigneron, R. Méric, M. Larchevêque, A. Debal, G. Kunesch, P. Zagatti and M. Gallois, Tetrahedron Lett., (1982), 23, 5051; f) J.P. Vigneron, R. Méric, M. Larchevêque, A. Debal, J.Y. Lallemand, G. Kunesch, P. Zagatti and M. Gallois, Tetrahedron (1984), 40, 3521;

g) K. Suzuki, T. Ohkuma and G-i. Tsuchihashi, Tetrahedron Lett., (1985), 26, 861; h) M. Masuda and K.i-c. Nishimura, Chem. Lett., (1981), 1333; i) T. Uematsu, T. Uemura and K. Mori, Agric. Biol. Chem., (1983), 47, 597; j) Y. Yokoyama and M. Yunokihara, Chem. Lett., (1983), 1245; k) T.K. Chakraborty and S. Chandrasekaran, Tetrahedron Lett., (1984), 25, 2891; l) D.S. Matteson, K.M. Sadhu, and M.L. Peterson, J. Am. Chem. Soc., (1986), 108, 810; m) H.G. Davies, S.M.Roberts B.J. Wakefield and J. A. Winders, J. Chem. Soc., Chem. Commun., (1985), 1166. n) R.M. Ortuño, R. Mercé and J. Font, Tetrahedron Lett., (1986), 27, 2519; see also C. Jaime, R.M. Ortuño and J. Font, J. Org. Chem., (1986), 51, 3946; o) H. Frauenrath and T. Philipps, Tetrahedron (1986), 42, 1135; see also Liebigs Ann. Chem., (1985), 1951.

253. Eldana saccharina (Wlk.) is a major pest on sugar cane and maize in many African countries : P.R. Atkinson, J. Ent. Soc. Sth. Afr., (1980), 43, 171.

254. Rosefuran, a similar (furanoid) compound, has been synthesised from the related α -Oxoketenedithioacetals, from non-furanoid starting materials : R. Okazaki, Y. Negishi and N. Inamoto, J. Org. Chem., (1984), 49, 3819.

255. In a subsequent experiment when the ratio of α,β -to β,γ-unsaturated aldehyde was a lot closer (1:1.3), reaction with 306 produced both adducts in the ratio (respectively) 1:1.8. This was found not to be a problem in the subsequent hydrolysis step: 312 was formed cleanly without contamination.

256. a) Vinyl sulphides are hydrolysed by mercuric ion in aqueous acetonitrile : E.J. Corey and J.I. Shulman, ibid., (1970), 35, 777;
b) see ref. 203 and 221a); c) E.J. Corey and D.J.Beames J. Am. Chem. Soc., (1973), 95, 5829.

257. See ref. 201a) p.690, Section D and associated ref.

258. Thiol esters have become recently important due to their synthetic value in macrolide syntheses : see lit. cited in S. Masamune, G.S. Bates, and J.W. Corcoran, Angew. Chem., Int. Ed. Engl., (1977), 16, 585; see also C.M.J.Fox, S.V. Ley, A.M.Z. Slawin and D.J. Williams, J. Chem. Soc., Chem. Commun., (1985), 1805; and S.V.Ley and P.R. Woodward, Tetrahedron Lett., (1987), 28, 345. For tetronate/tetronic acid syntheses using thiol esters, see P.M. Booth, C.M.J. Fox and S.V.Ley, Tetrahedron Lett., (1983), 24, 5143.

259. a) M.J. Janssen in "The Chemistry of Carboxylic Acids and Esters", Ed., S. Patai, John Wiley and Sons, London, 1969, p. 705; b) R.E. Barnett, Acc. Chem. Res., (1973), 6, 41.

260. See ref. 259a), p.724.

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262. ref. 261 and D. Seebach, B.-T. Gröbel and R. Bürstinghaus, Synthesis, (1976), 121.

263. See R.Tanikaga, H.Yamashita, A.Kaji, Synthesis, (1986), 416 for a recent example of a typical procedure.

264. Ref. 178 reports an improved trans-specific Michael addition of lithium dimethyl cuprate, which affords (±) - 314 in 82% yield. We followed the procedure in ref. 199.

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267. M. Nakagawa, J. Saegusa, M. Tonozuka, M. Obi, M. Kiuchi, T. Hino and Y. Ban, Org. Synth., (1977), 56, 49; M. Nakagawa, M. Tonozuka, M. Obi, M. Kiuchi and T. Hino, Synthesis, (1974), 510 (gives IR, NMR, MS). For derivatives of 5,6-dihydro-2H-pyran-2-one see ref. 10c).

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benzaldehyde/piperidine or diethylamine; acetaldehyde/ piperidine or diethylamine; acrylonitrile/benzyl trimethyl ammonium hydroxide; and sodium amide/bromoethane; whereas potassium tert-butoxide resulted in geometric isomerization ; see ref. 283. We have demonstrated that DBU does not deprotonate 305 (ref.236), thus the failure of secondary amines in this instance is perhaps not surprising.

287. If we had started from 1,1,3-tris(methylthio)propene and methylsulphenylated it, we could indirectly synthesise the tetrakissulphur substituted propene via an allylic methylthio rearrangement : see ref. 127 for allylic rearrangement of the phenylthio group. For an acid-catalysed thioallylic rearrangement see P. Brownbridge and S. Warren, J. Chem. Soc., Perkin Trans. 1, (1976), 2125.

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for some of the adducts (with respect to PMA), all sprayed yellow/orange with palladium chloride.

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300. 359: t.l.c. Rf 0.17 (10% ethyl acetate/petroleum); IR 2570 (w, S-H) cm^{-1}; ^1H NMR δ (270 MHz) 7.47-7.32(5H, m, Ph), 5.86(1H, s, vinyl proton), 5.16(1H, s, CC<u>H</u>(Ph)O), 3.12-2.82(6H, m, 2 SCH_2(dithiane) and SCH_2; latter appears at δ 3.01 as a t, J 7Hz), 2.57(2H, q, J 7.4Hz, $CH_2C\underline{H}_2SH$), 2.35-2.17(2H, m, dithiane CH_2), 1.89(2H, quintet, J 7.1Hz, $SCH_2C\underline{H}_2CH_2SH$), 1.38(1H, t, J 8.1Hz,

CH_2SH); MS (C.I.) m/z (rel. intensity) 357 (15, $M^{+\cdot}$ + H), 356 (8, $M^{+\cdot}$), 249 (100, $M^{+\cdot} - C_3H_7S_2$).

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